United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/petitioned-substances

Document Type:

☒ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☐ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Petition to the National Organic Standards Board for Amending the National List of the USDA's National Organic Program to Remove the Current Annotation and Add "s" to the End of "Phosphate" for:

Potassium Phosphate

A Non-Organic Agricultural Substance Allowed in Processing

Submitted date: February 29, 2024

Prepared by:
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Item A.1— Indicate which section or sections the petitioned substance will be included on and/or removed from the National List.

Name of Petitioned Substance: Potassium Phosphate
Section: § 205.605(b), Nonagricultural (nonorganic) substances allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients)".

Item A.2 — OFPA Category - Crop and Livestock Materials

Not applicable –- Materials petitioned for use in organic handling or processing.

Item A.3 — Inert Ingredients

Not applicable – Materials petitioned for use are not synthetic inert ingredient intended for use in a pesticide product.

Item B — Information on the Substance Being Petitioned

Item B.1 – Substance Name

Material Name as Listed on the National List: Potassium Phosphate

Chemical Name	Common Name	Other Names
Potassium Phosphate, Monobasic	Monopotassium Phosphate (MKP)	Potassium Phosphate Monopotassium Monophosphate Potassium Dihydrogen Phosphate Phosphoric Acid, Monopotassium Salt
Potassium Phosphate, Dibasic	Dipotassium Phosphate (DKP)	Potassium Phosphate Dipotassium Hydrogen Phosphate Potassium Phosphate Dibasic Anhydrous Dipotassium Phosphate (Anhydrous) Dipotassium Monophosphate Dipotassium Acid Phosphate
Potassium Phosphate, Tribasic	Tripotassium Phosphate (TKP)	Potassium Phosphate Tripotassium Orthophosphate

Item B.2 – Petitioner and Manufacturer Information

This petition is being submitted by the International Food Additives Council (IFAC), on behalf of its member companies that produce potassium phosphates.

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Item B.3 – Intended or Current Use

Current Use:

Potassium phosphate is listed on the National List with the annotation: for use only in agricultural products labeled "made with organic (specific ingredients or food group(s)," prohibited in agricultural products labeled "organic".

Per the National Organic Standards Board Handling Subcommittee "Cumulative impact of phosphates in organic processed foods Discussion Document" from 2016 (Appendix I): Potassium phosphate is used as a pH control agent in milk products, as a nutrient supplement, sequestrant and emulsifier, a malting or fermentation aid, and a stabilizer and thickener.

Intended Use:

Potassium phosphates are versatile ingredients that perform numerous technical functions in foods. However, they cannot be used to their full potential with the current annotation that is limited to "made with organic" products. IFAC would like to remove the annotation and allow potassium phosphates to be used in all products labeled as "organic." As an agricultural ingredient (food additive), potassium phosphates can be utilized in the following ways:

- Use as a pH buffer, to adjust the pH to the desired level in various foods.
- Use in processed cheese products, both for pH buffering and also to interact with milk proteins to promote emulsification.
- Use in casein-based coffee creamers, to stabilize the protein layer and thus prevent syneresis and curdling of the protein when added to hot, acidic coffee or tea.
- Use in ice cream and frozen desserts as a protein stabilizer.
- Use as a mineral supplement in foods and beverages to provide potassium fortification.
- Use as a nutrient and buffer in fermentation operations.
- Use as a sequestrant in meat and poultry products to decrease the amount of cooked-out juices.
- Use as a partial substitute for sodium chloride or in combination with sodium phosphates to reduce sodium content in food products.
- Use to promote heat stability (acting as a chaperone) for whey proteins during thermal processing to prevent destabilization during processing and aggregation of the protein.
- Use in indirect Ultra High Temperature (UHT) systems aids in staving off fouling that can impact manufacturing efficiency.

Item B.4 – Intended Activities and Application Rate

Typical Use with Current Annotation:

- Coffee creamers / whiteners: 1 – 2 % of powder *(total phosphates in buffer system)*
- Whipped toppings: 0.02 – 1.0 % of liquid *(total phosphates in buffer system)*
- Ice cream or frozen desserts: 0.1 – 0.2 % *(total phosphates in buffer system)*
- Canned cream or cheese soups: 0.2 % *(total phosphates in buffer system)*
- Process cheese (and cheese food, cheese spread): 0.5 – 3.0 % *(total phosphates in buffer system)*
- Cheese sauce: 0.5 – 3.0% *(total phosphates in buffer system)*
- Dried milk-drink products: 2.0 % of milk solids
- High protein beverages: 0.02 – 0.25% *(weight/weight)*
- Plant based alternatives: .02 – 0.25% *(weight/weight)*

- Mineral supplements: Determined by the supplement level needed
    - *Note: The Adequate Intake (AI) level for potassium is 4.7 g / day, and the Dietary Reference Intake (RDI) for phosphorus is 0.7 – 1.25 g / day.*

Intended Use for Meat and Poultry Products:

The USDA Food Safety Inspection Service (FSIS) regulates meat- and poultry-containing foods and is responsible for determining the suitability of FDA-approved substances in meat and poultry products. Removing the current annotation for potassium phosphates will promote alignment with USDA FSIS standards for the safe and suitable use of potassium phosphates and permit the use in organic meat and poultry products. USDA FSIS lists allowed food ingredients at 9 CFR 424.21, which includes the following potassium phosphates:

- Dipotassium phosphate
    - To decrease the amount of cooked out juices.
    - Meat food products except where otherwise prohibited by the meat inspection regulations and poultry food products except where otherwise prohibited by the poultry products inspection regulations.
    - For meat food products, 5 percent of phosphate in pickle at 10 percent pump level; 0.5 percent of phosphate in meat food product (only clear solution may be injected into meat food product). For poultry food products, 0.5 percent of total product.
- Monopotassium phosphate
    - To decrease the amount of cooked out juices.
    - Meat food products except where otherwise prohibited by the meat inspection regulations and poultry food products except where otherwise prohibited by the poultry products inspection regulations.
    - For meat food products, 5 percent of phosphate in pickle at 10 percent pump level; 0.5 percent of phosphate in meat food product (only clear solution may be injected into meat food product). For poultry products, 0.5 percent of total product.
- Potassium tripolyphosphate
    - To decrease the amount of cooked out juices.
    - Meat food products except where otherwise prohibited by the meat inspection regulations and poultry food products except where otherwise prohibited by the poultry products inspection regulations.
    - 5 percent of phosphate in pickle at 10 percent pump level; 0.5 percent of phosphate in meat food product (only clear solution may be injected into meat food product). For poultry food products, 0.5 percent of total product.
- Potassium pyrophosphate
    - To decrease the amount of cooked out juices.
    - Meat food products except where otherwise prohibited by the meat inspection regulations and poultry food products except where otherwise prohibited by the poultry products inspection regulations.
    - 5 percent of phosphate in pickle at 10 percent pump level; 0.5 percent of phosphate in meat food product (only clear solution may be injected into meat food product). For poultry food products, 0.5 percent of total product.
- Potassium tripolyphosphate
    - To decrease the amount of cooked out juices.

- Meat food products except where otherwise prohibited by the meat inspection regulations and poultry food products except where otherwise prohibited by the poultry products inspection regulations.
- 5 percent of phosphate in pickle at 10 percent pump level; 0.5 percent of phosphate in meat food product (only clear solution may be injected into meat food product). For poultry food products, 0.5 percent of total product.

Intended Use for Reduced-Sodium Products:
On April 10, 2023 the FDA published the Proposed Rule "Use of Salt Substitutes To Reduce the Sodium Content in Standardized Foods" (Docket No. FDA-2022-N-2226). The Proposed Rule, if finalized, would amend FDA's definitions and standards of identity (SOI; the acronym is used to refer to both the singular "standard of identity" and the plural "standards of identity") that specify salt (sodium chloride) as a required or optional ingredient. The amendments would permit the use of safe and suitable salt substitutes to replace some or all of the salt used in the manufacture of standardized foods. If finalized, the Proposed Rule would support the FDA's efforts to reduce sodium content in standardized foods and may help to improve consumer dietary patterns by reducing sodium consumption. It would also allow food manufacturers the flexibility to use salt substitutes and allow for innovation in producing healthier standardized foods. Comments closed on August 8, 2023. As of November 27, 2023 the FDA has not published a determination on finalization of the Proposed Rule.

Removing the current annotation for potassium phosphates would allow for food manufacturers in the organic sector to also be able to utilize potassium phosphates to reduce sodium content in organic food products labeled "Made with Organic Ingredients" and "Organic".

Item B.5 – Manufacturing Process
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.6 – Ancillary Substances
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.7 – Previous Reviews
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.8 – Regulatory Authority Provide information regarding EPA, FDA, and State regulatory authority registrations, including registration numbers.
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.9 – Chemical Abstracts Service (CAS) Number and Product Labels
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.10 – Physical and Chemical Properties
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.11 – Safety Information
Not applicable – This petition is to change an annotation for a substance that is already on the National List.

Item B.12 – Research Information

There are many factors to consider when choosing what ingredient(s) to use for buffering and/or stabilization of a food product. Additionally, there are many buffering agents that can be used to adjust pH, but their effectiveness for this purpose will depend on their form (e.g – acidic, basic, dibasic, tribasic), the pH trying to be obtained, the strength (pK_a) of the acid anion, and the molecular (equivalent) weight. Additional information on phosphates and their uses can be found below and in Addenda I.

Phosphates:

- MKP/MSP are good for lowering pH of products greater than a pH of 9
- DKP/DSP are good for raising the pH of products less than a pH of 4
- TSKP/TSP are good for raising the pH of products less than a pH of 9

In non-organic food products, sodium phosphates can often be used interchangeably with potassium phosphates. However, it may be necessary for manufacturers to substitute potassium phosphates for sodium phosphates in order to achieve sodium reduction goals as described previously. Expanding the permitted uses of potassium phosphates will give organic food manufacturers the same flexibility to create organic food products that meet both they and their customer's needs. Further, potassium phosphates have improved solubility compared to sodium phosphates, which is an additional formulation benefit for organic food manufacturers.

Salt (sodium chloride) may impart some of the same technical benefits as potassium phosphates in certain applications (for the reduction of cooked-out juices in meat, for example) however it lacks the multi-functionality that potassium phosphates provide beyond moisture retention, as they also act as a pH buffer, mineral supplement, sequestrant, and protein chaperone. Salt does not impart these same technical effects and therefore is not always an appropriate alternative.

The best alternatives to potassium phosphates are potassium citrate (in cheese) and potassium carbonate (in beverages). However, the due to the variance in pKa's the buffer capacity is not the same. Carbonate has 2 pKa's similar to TKP – both are slightly stronger acidity than corresponding phosphate, and forming CO2 in neutral solution can be a disadvantage. Citrate has 3 pKa's, all of which are more acidic and does not buffer where phosphate does. They can in theory be used at a 1:1 replacement to start, depending on how the pH is affected in each application. The key takeaway of this is that potassium citrates and potassium carbonates are alternatives, but each have a different buffering capacity and it will ultimately depend on where the starting pH is and what the desired pH will be with respect to buffering.

Item B.13. – Petition Justification Statement

I. Adding, amending, or removing an annotation for a listed substance (all sections) 7 C.F.R. §§ 205.605(b))

This petition is requesting:

- The removal of the current annotation: for use only in agricultural products labeled "made with organic (specific ingredients or food group(s)," prohibited in agricultural products labeled "organic".
- The addition of "s" to the end of potassium phosphate in the listing so that it aligns with the sodium phosphates and calcium phosphates listings.

The current annotation is outdated and unnecessarily limits the use of potassium phosphates in the organic food system. The current annotation does not allow food manufacturers to utilize potassium phosphates in the practical applications such as the previously stated use in meat and poultry products, plant-based creamers, and sodium-reduced products. Sodium-reduction is cited in this petition due to FDA's sodium reduction goals and initiative. FDA understands that in order for food manufactures to reduce sodium, they must replace it (fully or

partially) in food products with another ingredient that serve the same functional application; thus FDA's Proposed Rule "Use of Salt Substitutes To Reduce the Sodium Content in Standardized Foods" (Docket No. FDA-2022-N-2226). Additionally, changing the annotation would benefit to the organic product market as it would allow for organic products to participate in FDA's sodium reduction goals and initiative. For example, manufacturers would be able to opt to use Dipotassium Phosphate for plant-based creamers because it buffers their system very well and stabilizes the system but also has the added benefit of not increasing the sodium content in their creamer. While sodium phosphates and salt may be used as alternatives to potassium phosphates in some instances, they do not provide the same capacity for sodium reduction and, in the case of salt, have comparably limited functionality. Under the current annotation, a plant-based creamer could never be "Certified Organic", and at best can only make the claim to have been "made with Organic ingredients" even when all other ingredients are Certified Organic. This results in limiting manufacturers to "made with organic (specific ingredients or food group(s)," product labeling and needlessly excluding them from the ability to use potassium phosphates in "Organic" products.

Potassium phosphates (MKP, DKP, and TKP) are common food additives that have been available and used in the food industry for many years. The NOSB's 2016 Technical Report (Appendix II) acknowledges their safety as it states:

> *Each of the phosphate salts listed in the NOP regulations at 7 CFR 205.605(b) is identified by FDA in 21 CFR 182 as "Generally Recognized As Safe" (GRAS) for use in food for the various purposes shown below in Table 4 of the TR 2016. The only potassium phosphate salt that is the subject of a GRAS citation as a food ingredient is dipotassium phosphate. Nevertheless, monopotassium phosphate is permitted in frozen eggs (21 CFR 160.110(b)), and all of the potassium phosphates (mono-, di- and tripotassium) are GRAS for incidental food use in adhesives in articles intended for use in packaging, transporting or holding food (21 CFR 175.105). The USDA Food Safety Inspection Service (FSIS) permits both monopotassium phosphate and dipotassium phosphate in certain meat- and poultry-containing products (9 CFR 318.7 and 9 CFR 424.21).*

Potassium phosphates cannot be produced from a natural source and there are no organic substitutes.

Potassium phosphates are also included in some food standards of identity in Title 21 of the CFR, and allowed by the USDA in certain foods in Title 9 of the CFR. Citations included in these regulations are:

- 21 CFR 160.110(b) – MKP – (in Frozen eggs)
- 21 CFR 133.173(e)(1) – DKP – (in Pasteurized process cheese food)
- 21 CFR 133.169(c) – DKP – (in Pasteurized process cheese)
- 21 CFR 133.179(e) – DKP – (in Pasteurized process cheese spread)
- 9 CFR 424.21(c) – MKP and DKP – (in meat food products, to decrease the amount of cooked out juices)

Appendix I
Item B.12 – Research Information

1.The National Organic Standards Board Handling Subcommittee "Cumulative impact of phosphates in organic processed foods Discussion Document" August 16, 2016.
https://www.ams.usda.gov/sites/default/files/media/HSPhosphatesDiscDocNov2016.pdf

2. The National Organic Standards Board's 2016 Technical Report (Phosphates: calcium, potassium, sodium)
https://www.ams.usda.gov/sites/default/files/media/Phosphates%20TR%202_10_2016%20Final.pdf

3. "Use of Salt Substitutes To Reduce the Sodium Content in Standardized Foods". Federal Register. April 10, 2023. https://www.federalregister.gov/documents/2023/04/10/2023-06456/use-of-salt-substitutes-to-reduce-the-sodium-content-in-standardized-foods

4. Cooke, A. (2017), Dietary Food-Additive Phosphate and Human Health Outcomes. Comprehensive Reviews in Food Science and Food Safety, 16: 906-1021. https://doi.org/10.1111/1541-4337.12275.

5. Organic Trade Association. 2016 Docket: AMS-NOP-16-0049 Public Comments RE: Handling Subcommittee – Cumulative Impact of Phosphates in Organic Processed Foods (Discussion Document).
https://ota.com/sites/default/files/indexed_files/OTA_Phosphates_AMS-NOP-16-0049.pdf

6. EFSA FAF Panel (EFSA Panel on Food Additives and Flavourings), Younes, M, Aquilina, G, Castle, L, Engel, K-H, Fowler, P, Frutos Fernandez, MJ, Fürst, P, Gürtler, R, Husøy, T, Mennes, W, Moldeus, P, Oskarsson, A, Shah, R, Waalkens-Berendsen, I, Wölfle, D, Aggett, P, Cupisti, A, Fortes, C, Kuhnle, G, Lillegaard, IT, Scotter, M, Giarola, A, Rincon, A, Tard, A and Gundert-Remy, U, 2019. Scientific Opinion on the re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives and the safety of proposed extension of use. *EFSA Journal* 2019;17(6):5674, 156 pp. https://doi.org/10.2903/j.efsa.2019.5674

7.Gutiérrez OM. Sodium- and phosphorus-based food additives: persistent but surmountable hurdles in the management of nutrition in chronic kidney disease. Adv Chronic Kidney Dis. 2013 Mar;20(2):150-6. doi: 10.1053/j.ackd.2012.10.008. PMID: 23439374; PMCID: PMC3582990.

8. U.S. Food and Drug Administration. Sodium Reduction Website. https://www.fda.gov/food/food-additives-petitions/sodium-reduction

9. U.S. Food and Drug Administration. Guidance for Industry: Voluntary Sodium Reduction Goals. Docket Number:
FDA-2014-D-0055. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-voluntary-sodium-reduction-goals

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National Organic Standards Board
Handling Subcommittee
Cumulative impact of phosphates in organic processed foods
Discussion Document
August 16, 2016

I INTRODUCTION

Recent research indicates that phosphate intake has increased dramatically in the general population due to widespread use of phosphate food additives in processed foods in the United States. Consumers may be unaware of phosphorous levels when reading labels on products because phosphorous may not be disclosed on the nutrition panel. Phosphorous is an essential nutrient and deficiency is extremely rare. However, high levels of phosphates can result in a range of human health problems.

Outside the US and Canada, the only phosphate additive allowed in organic processed food is monocalcium phosphate, and only as a leavening agent.

During Sunset Review in 2015 the Handling subcommittee received public comment which included new research indicating potential serious human health impacts from the cumulative effects of phosphates which are added to processed foods. The NOSB evaluated the substances according to the criteria in OFPA, especially with regards Criteria 4, 6, and 7, and with reference to CFR 205.600(b) especially with regard 3 and 4. There was inadequate data to implicate any single phosphate, or any individual food item, as an isolated risk factor and thus the NOSB did not recommend that any of the phosphates be removed from the National List at Sunset. However the cumulative impact of these ingredients or processing aids remains an issue which merits further Discussion.

This Discussion Document outlines the issues and seeks public comment to determine the range of use of phosphates in organic processed foods, the extent to which they are really necessary, and to seek additional new medical and nutrition research on the human health impacts of these additives and their cumulative impact.

If public comment and associated research finding indicate need for further action, the NOSB may recommend increased restrictions through annotations or removal of phosphate food additives.

II BACKGROUND

In 2015, during its Review of Sunset 2017 materials, the NOSB received public comment, based on recent scientific research, raising concerns about the cumulative negative impact of phosphate food additives.

In July 2015, because several of the phosphates on the National List had not been fully reviewed in formal Technical Reports (TR), the NOSB requested a comprehensive TR to cover all the Phosphates, with particular emphasis on cumulative health impacts. The NOSB received this Technical Evaluation Report (TR) in February 2016. This TR did not include Tetrasodium pyrophosphate because a 2002 TR was already available and the material had been voted to be removed from the national list in April 2015.

The February 2016 TR presented a range of issues of concern which are further discussed below. However, at its October 2015 meeting in Stowe Vermont, while acknowledging the cumulative negative health impacts of phosphates, the NOSB voted to continue to list the phosphate materials as there was insufficient research to indicate that the tiny amounts of any one phosphate additive alone, as an isolated risk factor,

was sufficient to suggest removal from the List. The NOSB members and public comment indicated need for further discussion of this issue.

III RELEVANT AREAS OF THE RULE

Phosphate salts are allowed under the National Organic Program (NOP) Regulations at:

> 7 CFR 205.605 Nonagricultural (nonorganic) substances allowed as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))."
>
> The following nonagricultural substances may be used as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))" only in accordance with any restrictions specified in this section.
>
> 205.605(b) Synthetics allowed:
>
> **Calcium phosphate** (monobasic, dibasic, and tribasic).
>
> **Potassium phosphate**- for use only in agricultural products labeled "made with organic (specific ingredients or food group(s)," prohibited in agricultural products labeled "organic".
>
> **Sodium acid pyrophosphate** (CAS # 7758-16-9) –for use only as a leavening agent.
>
> **Sodium phosphates** – for use only in dairy foods.
>
> **Tetrasodium pyrophosphates** – (CAS # 7722-88-5) for use only in meat analog products. (This material was recommended by the NOSB, April 2015, for Removal from the National List and is presently in rulemaking).

The Organic Foods Production Act (OFPA) requires that the NOSB evaluate each substance according to 7 criteria as specified in 7 USC Section 6518(m) of the Act. The criteria of particular relevance to this discussion are:

(4) The effect of the substance on Human Health, and
(6) The alternatives to using the substance in terms of practices or other available materials and
(7) Compatibility with a system of sustainable agriculture.

In addition, CFR Section 205.600 (b) requires that any synthetic substance used as a processing aid or adjuvant will be evaluated against 6 additional criteria, where criteria 3, 4, 5, and 6 are particularly relevant to this discussion:

(1) The substance cannot be produced from a natural source and there are no organic substitutes;
(2) The substance's manufacture, use, and disposal do not have adverse effects on the environment and are done in a manner compatible with organic handling;
(3) The nutritional quality of the food is maintained when the substance is used, and the substance, itself, or its breakdown products do not have an adverse effect on human health as defined by applicable Federal regulations;
(4) The substance's primary use is not as a preservative or to recreate or improve flavors, colors, textures, or nutritive value lost during processing except where the replacement of nutrients is required by law;

(5) The substance is listed as generally recognized as safe (GRAS) by Food and Drug Administration (FDA) when used in accordance with FDA's good manufacturing practices (GMP) and contains no residues of heavy metals or other contaminants in excess of tolerances set by FDA; and
(6) The substance is essential for the handling of organically produced agricultural products.

IV DISCUSSION

1). Technical Reports:

It is clear that the NOSB has expressed concern about the health impacts of phosphates for a number of years, and requested several Technical Reports (TR), Technical Evaluation Reports (TR), and Technical Advisory Panel Reports (TAP). These reports have consistently included concerns for human health. The following TR and TAP are incorporated by reference herewith:

Calcium phosphate: TAP 1995 and TR Phosphates Feb 10, 2016;
Potassium phosphate: TAP 1995 and Phosphates TR Feb 10, 2016;
Sodium acid pyrophosphate: Sodium phosphates TAP Sept. 21, 2001, and SAP TR Sept 17, 2010 for rejected petition for expanded use in 2010, and Phosphates TR Feb 10, 2016;
Sodium phosphates: TAP Sept 21, 2001 and TR Phosphates Feb 10, 2016;
Tetrasodium pyrophosphate: TAP July 29, 2002; Limited scope TR June 9, 2014;

Note: These substances are also bioavailable sources of the nutrients calcium, phosphorus, potassium and sodium, and all but one are allowed by FDA as nutrient supplements in foods. However, their use as nutrient sources in foods labeled as organic is the subject of a separate Technical Report for Nutrient Vitamins and Minerals in 2015.

2). Uses of phosphate additives in processed products:

Phosphates are common additives found in many processed foods to increase shelf life, thicken, aid in gelling, stabilize, texturize, pH buffer, leavening etc. In recent years, as production of processed organic foods has increased, processors who typically produce non-organic foods, simply used some of the same additives as they expanded their production into organic. The result is widespread use of phosphate additives in organic processed foods.

(a) Phosphates in Organic foods

A survey and sampling of grocery stores in the Cleveland, Ohio area found that 44% of the best-selling grocery items contained phosphorus additives. The additives were particularly common in prepared frozen foods (72%), dry food mixes (70%), packaged meat (65%), bread and baked goods (57%), soup (54%), and yogurt (51%) categories.

Some companies produce the same or essentially the same organic product both with and without added phosphates. For example : Kraft Macaroni & Cheese Dinner™ is “organic” with added phosphate, and Kraft Organic Cheddar Macaroni & Cheese Dinner™ is produced without added phosphate.

Phosphorus additive-containing foods averaged 67 mg phosphorus per 100 g more than matched non-additive containing foods. Sample meals comprised mostly of phosphorus additive-containing foods had 736 mg more phosphorus per day compared to meals consisting only of additive-free foods. Phosphorus additive-free meals cost an average of $2.00 more per day (Leon, Sullivan, and Sehgal 2013) (TR 2016 lines 678-687)

Due to the present annotations on phosphate use in organic foods, it would be expected that basing a diet on organic foods would reduce the phosphorus intake. De Lorenzo et al. (2010) compared those

who ate an "Italian Mediterranean Organic Diet" to participants who followed a similar diet with phosphate additives and found reduced serum homocysteine and phosphorus levels, reduced microalbuminuria, and reduced cardiovascular disease risk in healthy individuals and in those with Chronic Kidney Disease (CKD). The results of this European trial cannot be extrapolated to the U.S. without some reservations. The EU organic regulations allow addition of only one phosphate, monocalcium phosphate, which can only be used as a leavening agent, whereas USDA organic regulations allow sodium pyrophosphate for this purpose and several other phosphates for other uses. These differences could be important, since Karp et al. (Karp, Ekholm, Kemi, Itkonen, et al. 2012) found that the conventional cereal product with the highest total phosphate content (216 mg/100 g), all of which was digestible, was industrial muffins that contained sodium acid pyrophosphate as the leavening agent. (TR 2016, 665-676)

(b) Specific phosphates and their uses.

Calcium phosphate *(monobasic, dibasic, and tribasic).*

Calcium phosphates are used in conventional foods as leavening agents, dough strengtheners and conditioners, nutrients, malting or fermenting aids and yeast foods (all three forms); the monobasic form is used as a buffer, firming agent and sequestrant; tribasic is used as an anticaking agent or free-flow agent, buffer or pH control agent, thickener or stabilizer. The NOP regulations at 7 CFR 205.605(b) do not impose additional restrictions on the use of calcium phosphates in processed organic foods. Tricalcium phosphate is commonly used in organic non-dairy beverages (soy 'milk', almond 'milk', orange juice, etc.) to provide the nutrients calcium and phosphorus. Dicalcium phosphate is the inert diluent and carrier for Vitamin B12 in fortified organic foods. Monocalcium phosphate is used as a component of chemical leavening agents ("baking powder"). Tricalcium phosphate is commonly used in non-dairy beverages as a source of calcium since these beverages displace cows' milk from the diet. Organic orange juice that is calcium-fortified contains tricalcium phosphate. Some organic yogurts and some non-dairy yogurt-like foods also contain tricalcium phosphate. Without this calcium fortification, these non-dairy beverages would be practically devoid of calcium.

Potassium phosphate*- for use only in agricultural products labeled "made with organic (specific ingredients or food group(s)," prohibited in agricultural products labeled "organic".*

Potassium phosphate is used as a pH control agent in milk products, as a nutrient supplement, sequestrant and emulsifier, a malting or fermentation aid, and a stabilizer and thickener. Dipotassium phosphate is the only form of potassium phosphate cited by FDA for use in pasteurized process cheese (21 CFR 133.169) and pasteurized process cheese food (21 CFR 133.173).

Sodium acid pyrophosphate *(CAS # 7758-16-9) –for use only as a leavening agent.*

Sodium acid pyrophosphate is used in conventional foods as a chemical leavening agent in baked goods; a sequestrant (chelating agent) to maintain the appearance of cooked and uncooked fruits and vegetables, particularly processed potatoes; an emulsifying agent and stabilizer in cheeses and related products; an inhibitor of struvite1 formation in canned tuna; and a curing accelerator in processed meat and poultry products.

Sodium phosphates *– for use only in dairy foods.*

Sodium phosphates are used in conventional foods as pH control agents and buffers, sequestrants, texturizers and nutrients. Monobasic sodium phosphate is used as an acidulant. Some organic products containing cheddar cheese, such as cheese crackers or macaroni and cheese, may contain organic cheddar cheese with added sodium phosphate.

Tetrasodium pyrophosphates *– (CAS # 7722-88-5) for use only in meat analog products*
Tetrasodium pyrophosphate (TSPP) is used as a synthetic food additive in the manufacture of meat substitutes (analogs) serving a number of purposes that compensate for insufficient gelling requirements. The effects of TSPP are to improve texture, adjust pH, act as a pH buffer, and reduce cooking loss. This material has been recommended for Removal from the National List

3). Approved Legal Uses of the Substance:
Each of the phosphate salts listed in the NOP regulations at 7 CFR 205.605(b) is identified by FDA in 21 CFR 182 as "Generally Recognized As Safe" (GRAS) for use in food for the various purposes shown below in Table 4 of the TR 2016. The only potassium phosphate salt that is the subject of a GRAS citation as a food ingredient is dipotassium phosphate. Nevertheless, monopotassium phosphate is permitted in frozen eggs (21 CFR 160.110(b)), and all of the potassium phosphates (mono-, di- and tripotassium) are GRAS for incidental food use in adhesives in articles intended for use in packaging, transporting or holding food (21 CFR 175.105). The USDA Food Safety Inspection Service (FSIS) permits both monopotassium phosphate and dipotassium phosphate in certain meat- and poultry-containing products (9 CFR 318.7 and 9 CFR 424.21).

FDA permits addition of sodium phosphates by name as an optional ingredient in several classes of dairy foods: pasteurized process cheese (21 CFR 133.169); pasteurized process cheese food (21 CFR 133.173); pasteurized process cheese spread (21 CFR 133.179); ice cream and frozen custard (21 CFR 135.110); and frozen eggs (21 CFR 160.110). The generic optional ingredient designation "stabilizer," which frequently is sodium or potassium phosphate, is permitted in a variety of dairy foods, such as acidified milk (21 CFR 131 131.111), cultured milk (21 CFR 131.112), evaporated milk (21 CFR 131.130), heavy cream (21 CFR 131.150), light cream (21 CFR 131.155), light whipping cream (21 CFR 131.157), eggnog (21 CFR 131.170), yogurt (21 133 CFR 131.200), and cream cheese (21 CFR 133.133).

Because most dairy foods naturally contain substantial amounts of both sodium and phosphorus from the milk, the small incremental amount of sodium and phosphorus contributed by a sodium phosphate stabilizer may exempt sodium phosphate from the requirement to be declared as an ingredient on the label. This practice is allowed by FDA at 21 CFR 101.100(a)(3)(ii)(b). The only FDA-regulated foods where this exemption from labeling is not permissible are hypoallergenic foods (21 CFR 105.62) and infant foods (21 CFR 105.65).

FSIS also requires labeling of all food additives for meat products. Thus, the absence of sodium phosphate from the ingredient declaration of an FDA-regulated food does not necessarily mean that this substance has not been added to the food.
FSIS regulates meat- and poultry-containing foods and is responsible for determining the suitability of FDA-approved substances in meat and poultry products. FSIS lists allowed food ingredients at 9 CFR 318.7 and 9 CFR 424.31. Phosphates, including sodium acid phosphates, trisodium phosphate, and mono- and dipotassium phosphates, are allowed at 9 CFR 319.180 in a variety of prepared meat-containing foods, particularly cooked sausage, which includes frankfurter, frank, hotdog, weiner, vienna sausage, bologna, knockwurst and similar products.

The NOP regulations at 7 CFR 205.605(b) restrict the use of sodium phosphates to organic dairy products only, so added phosphates are not permitted in prepared organic meat products .

4). International:
The Canadian Organic Standards align with the NOP regulations with regard to phosphates and the restrictions on their use. In contrast, the CODEX Guidelines, the European Regulation, the Japanese

Agricultural Standard and the IFOAM norms only allow monocalcium phosphate and only for use as a leavening agent.

5). Nutritional Value of Food (TR 2016 lines 346-405):

An important nutritional consideration of a diet is its calcium-to-phosphorus (Ca:P) ratio. During periods of rapid skeletal growth, such as in infancy, the dietary calcium-to- phosphorus ratio should not fall below 1.0. The FDA infant formula regulation (21 CFR 107.100(e)) requires a Ca:P ratio not less than 1.0 and not more than 2.0. In later life, calcium metabolism is closely regulated by Vitamin D metabolites, particularly calcitriol. High levels of blood phosphorus suppress the formation of calcitriol (Institute of Medicine 1997). The dangers of too much dietary phosphate include excessive bone loss and other effects.

The nutrient phosphorus is not subject to mandatory listing in the Nutrition Facts of a food label (21 CFR 101.9(c)(8)(ii)), and the ingredient declaration may not declare an added phosphate if exempted by 21 CFR 101.100(a)(3)(ii)(b). Consequently, 'silent' addition of phosphates as functional additives can alter the Ca:P ratio of food, and thus the diet, without the consumer being aware of the fact.

Sodium and potassium are two electrolyte minerals essential to life. Sodium and potassium interact nutritionally. Potassium salts are more expensive than their sodium counterparts, and potassium has a greater molecular weight than sodium, so a greater weight of potassium salts must be added. For these reasons, sodium phosphates are used far more frequently than are potassium phosphates in any application where the two are functionally interchangeable. However, since our diets in general provide much less potassium than is advised and much more sodium than is advised, using the potassium salt would be nutritionally advantageous. Note that sodium chloride (table salt) is the primary source of sodium in the diet and a much greater contributor of sodium to the American diet than the sodium phosphates (Institute of Medicine 2005).

6). Effects on Human Health: (see TR 2016 lines 438-687 and citations)

Phosphorus interacts with other mineral elements, particularly calcium, magnesium and potassium, in bone formation, kidney function, and other physiological processes. Understanding this interaction is important for understanding the effects of phosphates on human health and nutrition. The Ca:P ratio of a diet is important. The relation of these two well-known minerals to the lesser studied mineral magnesium is also important. Sodium also interacts with these mineral nutrients, particularly potassium.

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to continuously assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations and provides a correlation of nutrient intakes with health as well as socioeconomic status. The NHANES data provides a foundation base but it is understood that total phosphorus intake may be much higher.

The NHANES data on phosphorus, sodium, calcium and magnesium, and potassium intakes for adult American (~20 to ~50 years of age), compared to the dietary reference intakes for these nutrients, indicate the following for phosphorus:

Phosphorus: The Estimated Average Requirement (EAR) for adult men and women is 580 mg per day. The Recommended Dietary Allowance (RDA) is 700 mg per day and the Tolerable Upper Intake Level (UL) is 4000 mg per day (Institute of Medicine 1997). Mean daily intakes were reported as 1701 mg for men (243% of the RDA) and 1179 mg for women (168% of the RDA). The average intake of women in the lowest quartile of phosphorus intakes was reported as 671 mg per day, 15% greater than the EAR (Lee and Cho 2015). (TER, 2016, 464-469)

An analysis of NHANES data found that, after adjusting for demographics, cardiovascular risk factors, kidney function, and energy intake, a higher phosphorus intake was associated with higher all-cause mortality in individuals who consumed more than 1400 mg/day, but at intake levels less than 1400 mg/day, there was no association (Chang et al. 2014). Analysis of the NHANES data for individuals with moderate chronic kidney disease ("CKD") found that high dietary phosphorus intakes were not associated with increased mortality in moderate CKD (Murtaugh et al. 2012). A higher phosphorus intake was associated with higher calcium intake and was positively associated with bone mineral content in female teenagers, and it was also positively associated with bone mineral content and bone mineral density, as well as reduced risk of osteoporosis, in adults over 20 years of age (Lee and 490 Cho 2015). (TER 2016, 480-490)

7). Health effects of phosphorus provided by phosphate additives versus natural phosphorus in foods.

Elevated serum phosphate is a risk factor for certain diseases and disease outcomes. In healthy individuals, higher serum phosphate levels have been associated with greater risk for end-stage renal disease and mortality (Sim et al. 2013; Dominguez et al. 2013), abnormally low blood circulation (Meng et al. 2010), abnormally high arterial stiffness (Ix et al. 2009; Kendrick et al. 2010), increased risk of cardiovascular disease (Dhingra et al. 2007) and twice the risk of developing heart failure (Dhingra et al. 2010). Higher levels of serum phosphorus have also been shown to predict coronary artery disease development and progression (Tuttle and Short 2009).

Sodium and potassium phosphates and sodium acid pyrophosphate are very soluble in water. Consequently, the phosphorus in these additives, commonly referred to as "additive phosphorus," is immediately and completely bioavailable upon consumption. In contrast, the phosphorus naturally present in most foods ("food phosphorous") is much less available, in part due to the physical structure of the food and also because digestion of phosphate complexes may be required before the phosphorus can be absorbed.

The digestibility of phosphorus in various foods has been estimated by in vitro studies (Karp, Ekholm, Kemi, Hirvonen, et al. 2012; Karp, Ekholm, Kemi, Itkonen, et al. 2012). Only 6% of the phosphorus in sesame seeds with intact hulls was found to be digestible. In legumes, where much of the phosphorus is present as phytate, the average in vitro phosphorus digestibility was 38%. In contrast, the "additive phosphorus" in cola drinks and beer was 87-100% digestible. In cereal products the highest total phosphorus content and digestibility were found in industrial muffins containing "additive phosphorus" in the form of sodium pyrophosphate as a leavening agent.

8). Summary:

- The American diet provides very large amounts of phosphorus and sodium.
- The published phosphorus content is not based on analysis, so the amount of phosphorus consumed is understated.
- Half of the adult American population consumes less than the Estimated Average Requirement, EAR of magnesium and essentially no one nowadays consumes the Adequate Intake, AI of potassium.
- A substantial proportion of Americans, almost 40%, consume less than the EAR of calcium (Fulgoni et al. 2011).
- The major mineral content of the adult American diet is severely imbalanced.
- It is difficult to fully asses the health impacts of phosphate additives in processed organic foods, in part because scientific research typically focuses on one aspect of one material at a time. This allows the specific question posed in the research to be answered, but rarely allows for an understanding of the synergistic effects or cumulative impacts over time. A comprehensive meta-analysis may provide greater insight.

- Consumers typically do not calculate the total intake of every material as they eat their standard diet, both organic and conventional, processed or unprocessed, and often take additional mineral or nutritional supplements.
- The phosphate in phosphate additives is highly bioavailable and more potent for increasing blood phosphate levels than natural phosphate from food.
- High blood phosphate levels are associated with kidney and vascular disease.
- A sufficiently high intake of calcium appears to counteract some of the ill effects of excess dietary phosphorus but leads to an increased requirement for magnesium.

V REQUEST FOR PUBLIC COMMENT

The NOSB recognizes that although no single phosphate can be implicated as an isolated risk factor, it is clear that there are health implications from cumulative impact of phosphate additives in processed organic foods.
Please provide answers to the following questions:

1. If some brands of organic processed dairy products can be produced without use of phosphates, why not all of them? What are the alternatives?
2. If European, Japanese, CODEX and IFOAM standards limit phosphates to only monocalcium phosphate – only as a leavening agent, why are all the other phosphates necessary in U.S organic food processing?
3. Should phosphate food additives in processed organic foods be phased out, and if so should just some of them be phased out or should it be allowed in only some products?

Vote in Subcommittee

Motion to accept the discussion document on phosphates as written
Motion by: Jean Richardson
Seconded by: Ashley Swaffar
Yes: 7 No: 0 Recuse: 0 Absent: 1 Abstain: 0

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Identification of Petitioned Substances

This report addresses the following phosphate salts allowed under the National Organic Program (NOP) regulations at 7 CFR 205.605(b): calcium phosphates (monobasic, dibasic and tribasic), potassium phosphate, sodium acid pyrophosphate, and sodium phosphates. Chemical identifications of these phosphates are included in Table 1.

Table 1: Chemical Identification of the Phosphates Listed at 7 CFR 205.605(b).

Chemical Names	Chemical Formula	CAS Nos.	E/INS No.
Calcium phosphate, monobasic Calcium dihydrogen phosphate Calcium biphosphate Calcium bis(dihydrogen phosphate) Monocalcium phosphate Primary calcium phosphate Acid calcium phosphate Calcium diorthophosphate	$Ca(H_2PO_4)_2$ (anhydrous)	7758-23-8	E 341(i)
	$Ca(H_2PO_4)_2 \cdot 1\ H_2O$	10031-30-8	
Calcium phosphate, dibasic Calcium hydrogen phosphate Monocalcium acid phosphate Dicalcium orthophosphate	$CaHPO_4$ (anhydrous)	7757-93-9	E 341(ii)
	$CaHPO_4 \cdot 2\ H_2O$	7789-77-7	
Calcium phosphate, tribasic Tricalcium diphosphate Tricalcium phosphate Tricalcium orthophosphate	$Ca_3(PO_4)_2$ (anhydrous)	7758-87-4	E 341(iii)
Dipotassium phosphate (anhydrous) Dipotassium hydrogen phosphate Potassium hydrogen phosphate Potassium dibasic phosphate Potassium phosphate dibasic	K_2HPO_4 (anhydrous)	7758-11-4	E 340(ii)
	$K_2HPO_4 \cdot 3\ H_2O$	16788-57-1	
Sodium acid pyrophosphate (SAPP) Disodium diphosphate Disodium dihydrogen pyrophosphate; Diphosphoric acid, disodium salt	$Na_2H_2P_2O_7$ (anhydrous)	7758-16-9	E 450(vi)
Monosodium phosphate Sodium acid phosphate Sodium dihydrogen phosphate Sodium phosphate, monobasic	NaH_2PO_4 (anhydrous)	7558-80-7 7632-05-5	E 339(i)
	$NaH_2PO_4 \cdot 1\ H_2O$	10049-21-5	
	$NaH_2PO_4 \cdot 2\ H_2O$	13472-35-0	
Disodium phosphate Disodium hydrogen orthophosphate Disodium hydrogen phosphate Sodium phosphate, dibasic	Na_2HPO_4 (anhydrous)	7558-79-4	E 339(ii)
	$Na_2HPO_4 \cdot 2\ H2O$	10028-24-7	
	$Na_2HPO_4 \cdot 7\ H_2O$	7782-85-6	
	$Na_2HPO_4 \cdot 12\ H_2O$	10039-32-4	
Trisodium phosphate	Na_3PO_4 (anhydrous)	7601-54-9	E 339(iii)

Sodium phosphate, tribasic Sodium phosphate Sodium orthophosphate	$Na_3PO_4 \cdot 12\ H_2O$	10101-89-0	

Summary of Petitioned Use

This report addresses the following phosphate salts allowed under the National Organic Program (NOP) regulations at 7 CFR 205.605(b): calcium phosphates (monobasic, dibasic and tribasic), potassium phosphate, sodium acid pyrophosphate, and sodium phosphates. These substances are allowed as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))" unless otherwise specified by an annotation:

- Calcium phosphates (monobasic, dibasic, and tribasic) — no annotation
- Potassium phosphate—for use only in agricultural products labeled "made with organic (specific ingredients or food group(s))," prohibited in agricultural products labeled "organic"
- Sodium acid pyrophosphate (CAS # 7758-16-9)—for use only as a leavening agent
- Sodium phosphates—for use only in dairy foods

Several of these phosphate salts are available both as anhydrous substances (i.e., without water) and as hydrates. The hydrates have different physical properties from the anhydrous forms, which makes their use advantageous in certain applications.

These substances are also bioavailable sources of the nutrients calcium, phosphorus, potassium and sodium, and all but one are allowed by FDA as nutrient supplements in foods. However, their use as nutrient sources in foods labeled as organic is the subject of a separate Technical Report for Nutrient Vitamins and Minerals (OMRI 2015).

Characterization of Petitioned Substances

Composition of the Substance:

Chemical compositions of the phosphate salts address in this report are identified in Table 2.

Table 2: Chemical Composition of the Anhydrous Forms of the Phosphates Listed at 7 CFR 205.605(b).

Substance	Formula†	Phosphorus	Oxygen	Hydrogen	Metal
Calcium phosphate, monobasic	$CaHPO_4$	26.47%	54.69%	1.72%	17.12% calcium
Calcium phosphate, dibasic	$Ca(H_2PO_4)_2$	22.77%	47.04%	0.74%	29.46% calcium
Calcium phosphate, tribasic	$Ca3(PO_4)_2$	19.97%	41.27%	0%	38.76% calcium
Dipotassium phosphate	K_2HPO_4	17.78%	36.74%	0.58%	44.90% potassium
Sodium acid pyrophosphate	$Na_2H_2P_2O_7$	27.91%	50.49%	0.91%	20.72% sodium
Monosodium phosphate	NaH_2PO_4	25.82%	53.34%	1.68%	19.16% sodium
Disodium phosphate	Na_2HPO_4	21.82%	45.08%	0.71%	32.29% sodium
Trisodium phosphate	Na_3PO_4	18.89%	39.04%	0%	42.07% sodium

†anhydrous salt

Source or Origin of the Substances:

Sodium and potassium are isolated from brines or salt deposits. Calcium and phosphorus are sourced from limestone and phosphate rock, respectively. The food grade phosphates are formed by reacting purified phosphoric acid with sodium, potassium, or calcium hydroxides.

Phosphoric acid (H_3PO_4) is a triprotic acid, meaning that the phosphoric acid molecule has three protons (a proton is the positive hydrogen ion that characterizes an acid) that can dissociate from the molecule. Monobasic phosphates retain two hydrogen atoms; dibasic phosphates retain one hydrogen atom, and tribasic phosphates retain none.

Properties of the Substances:

Phosphates vary greatly in their solubility in water, ranging from the highly soluble sodium and potassium phosphates to practically insoluble bone ash (tricalcium phosphate). Phosphates also differ greatly in the pH values of their aqueous solutions. At high temperatures, many of the phosphates do not 'melt'; they decompose, forming pyrophosphates. Heating hydrated salts at relatively low temperatures (≤ 100°C) can drive off the water of hydration.

Table 3 below summarizes the major properties of phosphates allowed in organic handling. In the table, solubility is expressed in grams per 100 mL of water, generally at room temperature (20°-30°C) where such data are available. The pH is that of dilute aqueous solutions or slurries. Melting points ("MP") with the letter "d" indicate that the substance decomposes rather than melts. The data are drawn from the Merck Index (Budavari 1996), the Handbook of Chemistry and Physics, 40th Edition (Hodgman, Weast, and Selby 1959), U.S. government internet sources (e.g., PubChem Compound), and Material Safety Data Sheets (MSDS) of substance suppliers.

Table 3: Major Properties of the Phosphates Listed at 7 CFR 205.605(b).

Substance	Properties	Solubility	pH	MP °C
Calcium phosphate, monobasic	Crystalline; loses water of hydration at 100°C; decomposes at 200°C.	1.8	3.1 - 3.7	200 d*
Calcium phosphate, dibasic	White crystals; loses water of hydration at 109°C; upon ignition at 900°C forms calcium pyrophosphate.	0.02	7.0 – 8.0	900 d*
Calcium phosphate, tribasic	Amorphous, odorless, tasteless powder.	insoluble	insoluble	1670
Dipotassium phosphate	Anhydrous; white, somewhat hygroscopic granules; converted into potassium pyrophosphate by ignition.	167	8.5 - 9.6	d*
Sodium acid pyrophosphate	White, fused masses or crystalline powder. When heated to decomposition, it emits toxic fumes of phosphorus oxides and sodium oxide.	≥ 10	4.1 - 4.6	202 d*
Monosodium phosphate	Anhydrous salt is colorless; the monohydrate is white, odorless, slightly deliquescent crystals or granules; loses water of hydration at 100°C.	~100	4.5	204 d*
Disodium phosphate	Heptahydrate - crystals or granular powder; stable in air; loses five water molecules at 48°C.	104	9.1	d*
Trisodium phosphate	Dodecahydrate - colorless or white crystals, melts at ~75°C if heated rapidly.	14.5	11.9	1583

*d = decomposes

Specific Uses of the Substance:

Calcium phosphate (mono-, di-, and tribasic): The 1995 Technical Advisory Panel (TAP) review indicates that calcium phosphates are used in conventional foods as leavening agents, dough strengtheners and conditioners, nutrients, malting or fermenting aids and yeast foods (all three forms); the monobasic form is used as a buffer, firming agent and sequestrant; tribasic is used as an anticaking agent or free-flow agent, buffer or pH control agent, thickener or stabilizer (Technical Advisory Panel 1995a). The NOP regulations at 7 CFR 205.605(b) do not impose additional restrictions on the use of calcium phosphates in processed organic foods. Tricalcium phosphate is commonly used in organic non-dairy beverages (soy 'milk', almond 'milk', orange juice, etc.) to provide the nutrients calcium and phosphorus. Dicalcium phosphate is the inert diluent and carrier for Vitamin B_{12} in fortified organic foods. Monocalcium phosphate is used as a component of chemical leavening agents ("baking powder").

Potassium phosphate: The 1995 TAP review indicates that potassium phosphate is used as a pH control agent in milk products, as a nutrient supplement, sequestrant and emulsifier, a malting or fermentation aid, and a stabilizer and thickener (Technical Advisory Panel 1995b). Dipotassium phosphate is the only form of potassium phosphate cited by FDA for use in pasteurized process cheese (21 CFR 133.169) and pasteurized process cheese food (21 CFR 133.173). The NOP regulations at 7 CFR 205.605(b) limit the use of potassium phosphate to only those foods labeled "made with organic (specific ingredients or food group(s))."

Sodium acid pyrophosphate: The 2010 Technical Report indicates that sodium acid pyrophosphate is used in conventional foods as a chemical leavening agent in baked goods; a sequestrant (chelating agent) to maintain the appearance of cooked and uncooked fruits and vegetables, particularly processed potatoes; an emulsifying agent and stabilizer in cheeses and related products; an inhibitor of struvite[1] formation in canned tuna; and a curing accelerator in processed meat and poultry products (Technical Services Branch 2010). The NOP regulations at 7 CFR 205.605(b) limit the use of sodium acid pyrophosphate in organic foods to use only as a leavening agent. Sodium acid pyrophosphate is used as a component of chemical leavening agents ("baking powder").

Sodium phosphate (mono-, di-, and tribasic): The 2001 Technical Report indicates that sodium phosphates are used in conventional foods as pH control agents and buffers, sequestrants, texturizers and nutrients (OMRI 2001). Monobasic sodium phosphate is used as an acidulant. The NOP regulations at 7 CFR 205.605(b) restrict the use of sodium phosphates to organic dairy products only. Some organic products containing cheddar cheese, such as cheese crackers or macaroni and cheese, may contain organic cheddar cheese with added sodium phosphate.

Approved Legal Uses of the Substance:

Each of the phosphate salts listed in the NOP regulations at 7 CFR 205.605(b) is identified by FDA in 21 CFR 182 as "Generally Recognized As Safe" (GRAS) for use in food for the various purposes shown below in Table 4. Note that the only potassium phosphate salt that is the subject of a GRAS citation as a food ingredient is dipotassium phosphate. Nevertheless, monopotassium phosphate is permitted in frozen eggs (21 CFR 160.110(b)), and all of the potassium phosphates (mono-, di- and tripotassium) are GRAS for incidental food use in adhesives in articles intended for use in packaging, transporting or holding food (21 CFR 175.105). The USDA Food Safety Inspection Service (FSIS) permits both monopotassium phosphate and dipotassium phosphate in certain meat- and poultry-containing products (9 CFR 318.7 and 9 CFR 424.21).

Table 4: FDA GRAS References, Allowed Uses, and NOP Restrictions of Phosphate Salts.

[1] Struvite is a crystal composed of magnesium, ammonium and phosphate, three mineral elements that naturally occur in fish. The three elements react during the canning (sterilization) process to form crystals. The crystals look like tiny, sharp pieces of glass stuck inside the layers of canned tuna, causing consumer alarm.

Substance	FDA GRAS Reference	FDA Allowed Uses	NOP Restriction (7 CFR 205.605(b))
Calcium phosphate, monobasic	21 CFR 182.1217 21 CFR 182.6215 21 CFR 182.8217	Multiple Purposes* Sequestrant Nutrient	No restriction
Calcium phosphate, dibasic	21CFR 182.1217 21 CFR 182.8217	Multiple Purposes* Nutrient	No restriction
Calcium phosphate, tribasic	21CFR 182.1217 21 CFR 182.8217	Multiple Purposes* Nutrient	No restriction
Dipotassium phosphate	21 CFR 182.6285	Sequestrant	For use only in agricultural products labeled "made with organic (specific ingredients or food group(s))," prohibited in agricultural products labeled "organic"
Sodium acid pyrophosphate	21 CFR 182.1087	Multiple Purposes*	For use only as a leavening agent
Monosodium phosphate	21 CFR 182.1778 21 CFR 182.6085 21 CFR 182.6778 21 CFR 182.8778	Multiple Purposes* Sequestrant Sequestrant Nutrient	For use only in dairy foods
Disodium phosphate	21 CFR 182.1778 21 CFR 182.6290 21 CFR 182.6778 21 CFR 182.8778	Multiple Purposes* Sequestrant Sequestrant Nutrient	For use only in dairy foods
Trisodium phosphate	21 CFR 182.1778 21 CFR 182.6778 21 CFR 182.8778	Multiple Purposes* Sequestrant Nutrient	For use only in dairy foods

* The prior TAP reviews and Technical Reports cited in the section *Specific Uses of the Substance* above enumerate the multiple purposes in conventional foods.

FDA permits addition of sodium phosphates by name as an optional ingredient in several classes of dairy foods: pasteurized process cheese (21 CFR 133.169); pasteurized process cheese food (21 CFR 133.173); pasteurized process cheese spread (21 CFR 133.179); ice cream and frozen custard (21 CFR 135.110); and frozen eggs (21 CFR 160.110). The generic optional ingredient designation "stabilizer," which frequently is sodium or potassium phosphate, is permitted in a variety of dairy foods, such as acidified milk (21 CFR 131.111), cultured milk (21 CFR 131.112), evaporated milk (21 CFR 131.130), heavy cream (21 CFR 131.150), light cream (21 CFR 131.155), light whipping cream (21 CFR 131.157), eggnog (21 CFR 131.170), yogurt (21 CFR 131.200), and cream cheese (21 CFR 133.133).

Because most dairy foods naturally contain substantial amounts of both sodium and phosphorus from the milk, the small incremental amount of sodium and phosphorus contributed by a sodium phosphate stabilizer may exempt sodium phosphate from the requirement to be declared as an ingredient on the label. This practice is allowed by FDA at 21 CFR 101.100(a)(3)(ii)(b). The only FDA-regulated foods where this exemption from labeling is not permissible are hypoallergenic foods (21 CFR 105.62) and infant foods (21 CFR 105.65). FSIS also requires labeling of all food additives for meat products. Thus, the absence of sodium phosphate from the ingredient declaration of an FDA-regulated food does not necessarily mean that this substance has not been added to the food.

FSIS regulates meat- and poultry-containing foods and is responsible for determining the suitability of FDA-approved substances in meat and poultry products. FSIS lists allowed food ingredients at 9 CFR 318.7 and 9 CFR 424.31. Phosphates, including sodium acid phosphates, trisodium phosphate, and mono- and dipotassium phosphates, are allowed at 9 CFR 319.180 in a variety of prepared meat-containing foods,

particularly cooked sausage, which includes frankfurter, frank, hotdog, weiner, vienna sausage, bologna, knockwurst and similar products. The NOP regulations at 7 CFR 205.605(b) restrict the use of sodium phosphates to organic dairy products only, so added phosphates are not permitted in prepared organic meat products .

Action of the Substances:

Anticaking Agent and Free-Flow Agent: Anhydrous tricalcium phosphate is an effective carrier for vitamin and mineral premixes and other dry mixes because it is insoluble, non-hygroscopic, and chemically inert except in acidic environments. In an acidic environment, such as the normal stomach, tricalcium phosphate slowly dissolves, providing the nutrients calcium and phosphorus in nutritionally desirable proportions. Dicalcium phosphate (anhydrous dibasic calcium phosphate) is used for similar purposes.

pH Control, Buffering: Phosphate is a trivalent anion and the basis for many chemical buffers. A buffered solution can tolerate the addition of acid or alkali with minimal change in pH. Many liquid foods are very sensitive to pH. For example, adding acid and reducing the pH of milk can cause the protein casein to precipitate. (This is how cottage cheese is produced.) The pH is very important for ensuring food safety. Bacteria such as *Clostridium botulinum* will not grow or produce toxin in foods with a pH of 4.6 or lower. Decreasing and maintaining the pH to less than 4.6 can be achieved with a food-safe acidulant such as monobasic calcium phosphate or monosodium phosphate, which also can act as a buffer to prevent the food from becoming too acidic and changing the flavor profile. The two most commonly used food buffering systems are those based on phosphate and on citrate.

Non-Yeast Leavening: Monobasic calcium phosphate and sodium acid pyrophosphate are acidulants routinely combined with sodium bicarbonate (commonly called "baking soda") to create leavening mixtures (commonly called "baking powder"). The pH of a monobasic calcium phosphate solution is between 3.1 and 3.7, and the pH of a sodium acid pyrophosphate solution is between 4.1 and 4.6. Monobasic calcium phosphate and sodium acid pyrophosphate are stable powders at room temperature that can be mixed with baking soda and remain chemically stable in the dry state, even when mixed with dry baking ingredients such as flour. When fluid is added to make the dough, and the dough is put into a hot oven to bake, the leavening components dissolve and react chemically to liberate carbon dioxide gas. This gas leavens the dough and generates the desired 'airy' texture of the baked goods.

Monocalcium phosphate is used as the single acidulant in some aluminum-free baking powder products. Some baking powders, called "double-action baking powder," contain a second acidulant, either sodium acid pyrophosphate or sodium aluminum sulfate. Neither of these acidulants reacts with sodium bicarbonate until they are wet and hot. In practical terms, sodium acid pyrophosphate and sodium aluminum sulfate do not start reacting with the sodium bicarbonate until after the dough or batter is in the oven. This means that the batter rises for a longer period of time, making lots of bubbles and a fluffier cake, muffin, etc. (Shipman 2014). Note that aluminum sulfate is not allowed in organic processing.

Milk Protein Stabilization: The phosphates in sodium phosphate and potassium phosphate interact with milk proteins, such as casein, to function as emulsifiers that prevent the separation of fat and water in cheese (Gard 1996). These phosphates also stabilize milk and cheese by chelating ("sequestering") calcium (Scharpf 1971). The addition of sodium phosphate to evaporated milk prevents the separation of butterfat and aqueous phases and prevents gel formation (Molins 1991). Separated fat and protein can form an insoluble, non-dispersible layer (Webb, Deysher, and Potters 1951). Disodium phosphate also is used as a processing agent in heavy whipping cream, where it binds to milk minerals to prevent the milk from coating the equipment during processing. Sodium phosphates are used in some pasteurized organic milk products, such as half-and-half and whipping cream, to stabilize the milk protein and to ensure the products do not separate or lose protein prior to consumer use.

Combinations of the Substance:
Most aluminum-free baking powder used in the home is a mixture of monocalcium phosphate, corn starch carrier, and sodium bicarbonate (baking soda).

Status

Historic Use:
The most common historical use of sodium phosphates consistent with 7 CFR 205.605(b) is for stabilizing evaporated milk and similar fluid milk products, and stabilizing processed cheese. The use of phosphate emulsifiers in cheese apparently began about 1895 (Heidolph and Gard 2000; Corbridge 2013).

Organic Foods Production Act, USDA Final Rule:
The NOP regulations include the following listings of phosphate salts at 7 CFR 205.605(b):

- Calcium phosphates (monobasic, dibasic and tribasic)
- Potassium phosphate—for use only in agricultural products labeled "made with organic (specific ingredients or food group(s))," prohibited in agricultural products labeled "organic"
- Sodium acid pyrophosphate (CAS # 7758-16-9)—for use only as a leavening agent
- Sodium phosphates—for use only in dairy foods

The NOP regulations also include a listing for "nutrient vitamins and minerals" at 7 CFR 205.605(b) which includes phosphates. The use of phosphates as a nutrient source in organic foods is the subject of a separate Technical Report (OMRI 2015).

International
The Canadian Organic Standards align with the NOP regulations with regard to the phosphate salts addressed in this report and the restrictions on their use. In contrast, the CODEX Guidelines, the European Regulation, the Japanese Agricultural Standard and the IFOAM norms only allow monocalcium phosphate and only for use as a leavening agent.

Canada
The Canadian General Standards Board Permitted Substances List (CAN/CGSB 32.311-2006) permits these phosphate salts with usage annotations identical to the NOP regulations.

CODEX Alimentarius Commission Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)
These guidelines only permit monocalcium phosphate (341(i)) and "only for raising flour" (as a leavening agent).

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008
ANNEX VIII, Certain products and substances for use in production of processed organic food referred to in Article 27(1)(a), Section A – Food Additives, including Carriers, lists only monocalcium phosphate (341(i)) as a "Raising agent for self-raising flour" (as a leavening agent).

Japanese Agricultural Standard for Organic Processed Foods (Notification No. 1606 of the Ministry of Agriculture, Forestry and Fisheries of October 27, 2005)
Table 1, "Food Additives," lists INS 341(i), Calcium dihydrogen phosphate (a.k.a. monocalcium phosphate), with the annotation "Limited to be used for powders as expanding agent" (as a leavening agent).

IFOAM – Organics International (IFOAM)
The IFOAM norms for Organic Production and Processing, Version 2014, list monocalcium phosphate, INS 341, as a food additive "Only for 'raising flour'"(as a leavening agent).

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: Describe the most prevalent processes used to manufacture or formulate the petitioned substances. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substances when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

The phosphate salts addressed in this report are formed by combining aqueous solutions of phosphoric acid with either calcium hydroxide (or calcium carbonate), potassium hydroxide, or sodium hydroxide (or sodium carbonate). Manufacturing processes for phosphates and the raw materials are described in Table 5.

Table 5. Manufacturing Processes for Food Grade Phosphates and their Raw Materials.

Phosphoric acid	Phosphoric acid is produced by treating phosphate rock (tricalcium phosphate) with sulfuric acid, forming phosphoric acid and calcium sulfate (Budavari 1996).
Calcium hydroxide	Calcium hydroxide is produced by the hydration of lime (calcium oxide) (21 CFR 184.1205). Calcium oxide is produced from calcium carbonate, limestone or oyster shells by calcination at temperatures of 925° to 1350 °C (21 CFR 184.1210).
Calcium carbonate	Calcium carbonate is prepared by three common methods of manufacture: (1) as a byproduct in the "lime soda process" (adding lime (calcium oxide) and sodium carbonate to hard water precipitates calcium as the carbonate); (2) by precipitation of calcium carbonate from calcium hydroxide in the "carbonation process"; or (3) by precipitation of calcium carbonate from calcium chloride in the "calcium chloride process" (21 CFR 184.1191).
Calcium phosphate, monobasic	Monobasic calcium phosphate is produced by treating calcium hydroxide with phosphoric acid.
Calcium phosphate, dibasic	Dibasic calcium phosphate is produced by the reaction of phosphoric acid, calcium chloride, and sodium hydroxide. Calcium carbonate can be used in place of the calcium chloride and sodium hydroxide.
Calcium phosphate, tribasic	Tricalcium phosphate for food use is prepared from phosphoric acid and calcium hydroxide. Tricalcium phosphate is extremely insoluble in water, so in order to avoid settling in liquid nutritional formulations, calcium phosphate can be formed *in situ* as a colloidal, hydrated gel by adding concentrated phosphoric acid to a dilute solution of calcium hydroxide (Lin and Cho 1987).
Potassium hydroxide	Potassium hydroxide is obtained commercially by electrolysis of a potassium chloride solution in the presence of a porous diaphragm (21 CFR 184.1631).
Dipotassium phosphate	All orthophosphate derivatives of potassium can be generated by neutralization of phosphoric acid with potassium hydroxide (Budavari 1996).
Sodium hydroxide	Sodium hydroxide is prepared commercially by electrolyzing a sodium chloride solution or by reacting calcium hydroxide with sodium carbonate (21 CFR 184.1763).
Sodium carbonate	Sodium carbonate is produced (1) from purified trona ore that has been calcined to soda ash; (2) from trona ore calcined to impure soda ash and then purified; or (3) by synthesis from limestone in the Solvay process (21 CFR 184.1742).
Sodium acid pyrophosphate	Sodium carbonate is reacted with phosphoric acid to form monosodium phosphate, followed by heating the monosodium carbonate to 220°C to form sodium acid pyrophosphate (U.S. National Library of Medicine 2002).
Monosodium phosphate	All of the orthophosphate derivatives of sodium can be generated by neutralizing phosphoric acid with sodium hydroxide (Budavari 1996).
Disodium phosphate	

Trisodium phosphate	

Evaluation Question #2: Discuss whether the petitioned substances are formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)). Discuss whether the petitioned substances are derived from an agricultural source.

The phosphate salts addressed in this report are made by the chemical processes described above, all of which involve the simple reaction of a mineral acid (phosphoric acid) with an alkaline substance such as calcium hydroxide or calcium carbonate, potassium hydroxide, or sodium hydroxide or sodium carbonate.

Evaluation Question #3: If the substances are synthetic substances, provide a list of nonsynthetic or natural source(s) of the petitioned substances (7 CFR § 205.600 (b) (1)).

Rock phosphate is a natural source of tricalcium phosphate. However, rock phosphate contains radionuclides in concentrations that are 10 to 100 times the radionuclide concentration found in most natural materials (Menzel 1968). Most of the radionuclides consist of uranium and its decay products. Some rock phosphate also contains elevated levels of thorium and its daughter products. The specific radionuclides of significance include uranium-238, uranium-234, thorium-230, radium-226, radon-222, lead-210, and polonium-210 (Menzel 1968). Another impurity of concern is fluorine, which can interfere with calcium and bone metabolism (Rama Rao and Reddy 2001). For food use, purified food grade materials must be used.

Evaluation Question #4: Specify whether the petitioned substances are categorized as generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices (7 CFR § 205.600 (b)(5)).

All of the phosphate salts addressed in this report are GRAS. See Table 4 for regulatory references.

Evaluation Question #5: Describe whether the primary technical function or purpose of the petitioned substances is a preservative. If so, provide a detailed description of its mechanism as a preservative (7 CFR § 205.600 (b)(4)).

None of the phosphate salts addressed in this report are preservatives when used in accordance with 7 CFR 205.605(b). They have no killing effects on bacteria, fungi, mold or yeast. To the contrary, these sources of the nutritionally essential elements phosphorus, calcium, potassium and sodium are used as components of yeast food and bacterial culture media. In some meat- and poultry-containing processed foods, sodium acid pyrophosphate is used to accelerate color fixing or to preserve color during storage of cured pork and beef cuts, cured poultry, and cured comminuted poultry and meat food products. However, in organic foods, sodium acid pyrophosphate is permitted solely for leavening, so this color-fixing use is not permitted.

Evaluation Question #6: Describe whether the petitioned substances will be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law) and how the substances recreate or improve any of these food/feed characteristics (7 CFR § 205.600 (b)(4)).

Sodium acid pyrophosphate is used as a leavening agent in baked goods, where it reacts with baking soda (sodium bicarbonate) to liberate carbon dioxide, 'leavening' the dough and creating the desired 'airy' texture that consumers expect of baked goods such as cakes and cookies. Monobasic calcium phosphate also is used as a leavening agent in household aluminum-free baking powder and in processed organic

foods such as pancake and waffle mixes, cookies and crackers. Thus, the use of these phosphates as leavening agents improves the texture of these baked foods.

Potassium phosphate and sodium phosphates are used in evaporated milk and other milk products to prevent fat and protein separation and thus prevent the loss of the nutritional value of the fat and protein (and accompanying calcium and other minerals) that occur post-processing during product storage. Thus, this use of phosphates helps to retain nutritive value and pre-processing physical properties, rather than recreating or improving them.

Tricalcium phosphate is commonly used in non-dairy beverages as a source of calcium since these beverages displace cows' milk from the diet. Organic orange juice that is calcium-fortified contains tricalcium phosphate. Some organic yogurts and some non-dairy yogurt-like foods also contain tricalcium phosphate. Without this calcium fortification, these non-dairy beverages would be practically devoid of calcium.

Evaluation Question #7: Describe any effect or potential effect on the nutritional quality of the food or feed when the petitioned substances are used (7 CFR § 205.600 (b)(3)).

An important nutritional consideration of a diet is its calcium-to-phosphorus (Ca:P) ratio. The chemical information in Table 2 can be used to calculate this ratio for the phosphates allowed in 7 CFR 205.605(b). The Ca:P ratios in the three calcium phosphates vary from 0.65:1 for the monobasic salt to 1.3:1 for the dibasic salt to 1.9:1 for the tricalcium phosphate. The calcium-free sodium and potassium phosphates have a Ca:P ratio of zero. During periods of rapid skeletal growth, such as in infancy, the dietary calcium-to-phosphorus ratio should not fall below 1.0. The FDA infant formula regulation (21 CFR 107.100(e)) requires a Ca:P ratio not less than 1.0 and not more than 2.0. In later life, calcium metabolism is closely regulated by Vitamin D metabolites, particularly calcitriol. High levels of blood phosphorus suppress the formation of calcitriol (Institute of Medicine 1997). The dangers of too much dietary phosphate include excessive bone loss and other effects noted below.

The nutrient phosphorus is not subject to mandatory listing in the Nutrition Facts of a food label (21 CFR 101.9(c)(8)(ii)), and the ingredient declaration may not declare an added phosphate if exempted by 21 CFR 101.100(a)(3)(ii)(b). Consequently, 'silent' addition of phosphates as functional additives can alter the Ca:P ratio of food and thus the diet without the consumer being aware of the fact.

Sodium and potassium are two electrolyte minerals essential to life. Sodium and potassium interact nutritionally. Potassium salts are more expensive than their sodium counterparts, and potassium has a greater molecular weight than sodium, so a greater weight of potassium salts must be added. For these reasons, sodium phosphates are used far more frequently than are potassium phosphates in any application where the two are functionally interchangeable. However, since our diets in general provide much less potassium than is advised and much more sodium than is advised, using the potassium salt would be nutritionally advantageous. Note that sodium chloride (table salt) is the primary source of sodium in the diet and a much greater contributor of sodium to the American diet than the sodium phosphates (Institute of Medicine 2005).

Some highly processed conventional dairy foods, such as pasteurized process cheese food (21 CFR 133.173), a product with a moisture content of not more than 44% (i.e., not less than 56% solids), may contain up to 3% of the wet weight of the cheese food as sodium phosphate (anhydrous basis). Consequently, the additive sodium phosphate may represent more than 5% of the total solids in this food. Nevertheless, the phosphorus content of the process cheese food may be very similar to that of a natural cheese. Below in Table 7 is a partial nutritional comparison of two slices of pasteurized process American cheese food and the same weight of a natural cheese such as Monterey cheese, using standard values of the USDA National Nutrient Database for Standard Reference. In contrast to the minor difference in total phosphorus content, the sodium content of the process cheese food is over twice that of the natural cheese. Note that the process

cheese food provides three times as much potassium as the natural cheese does, since process cheese food normally includes whey and milk solids among its ingredients.

Table 7: Comparison of the Nutrient Content of Pasteurized Process Cheese Food and Monterey Cheese.

Product	Total Weight	Water	Protein	Fat	Calcium	Phosphorus	Potassium	Sodium
Process American cheese food, two ¾-oz. slices	42 g	18.5 g	7.08 g	10.76 g	286 mg	184 mg	107 mg	539 mg
Monterey cheese, 42 grams	42 g	17.2 g	10.28 g	12.72 g	313 mg	186 mg	34 mg	252 mg

A more direct comparison of the nutritional effects of added sodium phosphate can be gleaned from a compositional comparison of stabilized evaporated milk and the calorically equivalent amount of fresh milk as shown in Table 8.

Table 8: Comparison of the Nutrient Content of Evaporated Milk and Whole Milk.

Product	kcal	Protein	Fat	Calcium	Phosphorus	Ca:P ratio	Potassium	Sodium
Evaporated milk, 16 fl. oz. (504 g)	675	34.32 g	38.10 g	1315 mg	1023 mg	1.285	1527 mg	534 mg
Whole milk	675	34.84 g	35.94 g	1250 mg	929 mg	1.346	1460 mg	476 mg

The Ca:P ratio of whole milk is about 5% greater than that of evaporated milk. Assuming that the same supply of whole milk was the raw material for both products, the milk contribution of phosphorus to the evaporated milk would be 977 mg, compared to the database value of 1023 mg, suggesting that about 46 mg of phosphorus has been contributed by sodium phosphate stabilizer. Early work on the stabilization of evaporated milk indicated that an addition of 4 to 10 oz (113 to 284 g) of crystalline disodium phosphate (heptahydrate = 11.56% P) per 1000 lb (454 kg) of evaporated milk was effective in most situations, but as much as 16 oz. of disodium phosphate were required in unusual circumstances (Sommer and Hart 1926). These amounts of disodium phosphate would contribute 14 to 36 to 58 mg of phosphorus per 16 fl oz of evaporated milk, amounts which bracket the estimate of 46 mg of phosphorus calculated from the compositional comparison. Thus, the assumption that phosphate addition reduces the Ca:P ratio of evaporated milk by about 5% is reasonable. The sodium phosphate addition level estimated from the phosphorus differential is equivalent to about 12 oz per 1000 lb. The estimate for the addition level based on the sodium differential is about 11 oz per 1000 lb of evaporated milk. Thus, the amount of sodium phosphate used to stabilize evaporated milk has changed little in 90 years.

<u>Evaluation Question #8:</u> List any reported residues of heavy metals or other contaminants in excess of FDA tolerances that are present or have been reported in the petitioned substances (7 CFR § 205.600 (b)(5)).

The Food Chemicals Codex, originally created by the Food Protection Committee, National Academy of Sciences - National Research Council and now published by the United States Pharmacopeial Convention, provides FDA-recognized standards for these purified and chemically defined food additives. The 1996 Food Chemicals Codex specifications for these phosphates included limits for arsenic of not more than 3 mg/kg, for fluoride of not more than 0.005%, and for heavy metals, expressed as lead, of not more than 10 mg/kg. The 2010 Food Chemicals Codex (U. S. Pharmacopeia 2010) standards are listed in Table 9.

Table 9: Heavy Metals and Impurities in Food Grade Phosphates.

Substance	Fluoride	Arsenic	Lead
	Not more than		

Calcium phosphate, monobasic	0.005%	3 mg/kg	2 mg/kg
Calcium phosphate, dibasic	0.005%	3 mg/kg	2 mg/kg
Calcium phosphate, tribasic	0.0075%	3 mg/kg	2 mg/kg
Dipotassium phosphate	10 mg/kg	3 mg/kg	2 mg/kg
Sodium acid pyrophosphate	0.005%	3 mg/kg	2 mg/kg
Monosodium phosphate	0.005%	3 mg/kg	2 mg/kg
Disodium phosphate	0.005%	3 mg/kg	2 mg/kg
Trisodium phosphate	0.005%	3 mg/kg	2 mg/kg

Evaluation Question #9: Discuss and summarize findings on whether the manufacture and use of the petitioned substance may be harmful to the environment or biodiversity (7 U.S.C. § 6517 (c) (1) (A) (i) and 7 U.S.C. § 6517 (c) (2) (A) (i)).

Over 20 years ago, trisodium phosphate was used as a major component of detergents and alone as a robust cleaning agent. The result was that sodium and phosphate entered the waste water stream and eventually ended up in lakes, rivers and streams. The phosphate contributed by detergents caused algal blooms and eutrophication of the Great Lakes. This environmental disaster was remedied by the development of low-phosphate detergents, and by bans on high-phosphate detergents in the states where waterways drain into the Great Lakes (US Environmental Protection Agency 1997). Today most detergents are low in phosphate. This environmental damage was primarily related to sodium phosphate used as a detergent or cleaner, and has little bearing on the use of sodium phosphates as food additives, beyond confirming that sodium phosphates are bioavailable nutrient sources for growing microorganisms such as yeast and bacteria.

Evaluation Question #10: Describe and summarize any reported effects upon human health from use of the petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (i), 7 U.S.C. § 6517 (c) (2) (A) (i)) and 7 U.S.C. § 6518 (m) (4)).

Sodium and potassium phosphates are used widely in processed foods, and this evaluation question further explains how they can contribute a substantial amount of phosphorus to the American diet. Calcium phosphates contribute calcium, with Ca:P ratios of 0.65:1 for the monobasic salt, 1.3:1 for the dibasic salt, and 1.9:1 for tricalcium phosphate.

Nutritional status of the adult American population with respect to the major mineral nutrients

Phosphorus interacts with other mineral elements, particularly calcium, magnesium and potassium, in bone formation, kidney function, and other physiological processes. Understanding this interaction is important for understanding the effects of phosphates on human health and nutrition. As mentioned earlier, the Ca:P ratio of a diet is important. The relation of these two well-known minerals to the lesser studied mineral magnesium is also important. Sodium also interacts with these mineral nutrients, particularly potassium.

The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to continuously assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. The resulting database has been mined extensively by researchers to establish the correlation of nutrient intakes with health as well as socioeconomic status. The NHANES data on phosphorus, sodium, calcium and magnesium, and potassium intakes for adult American (~20 to ~50 years of age), compared to the dietary reference intakes for these nutrients, indicate the following:

Phosphorus: The Estimated Average Requirement (EAR) for adult men and women is 580 mg per day. The Recommended Dietary Allowance (RDA) is 700 mg per day and the Tolerable Upper Intake Level (UL) is

4000 mg per day (Institute of Medicine 1997). Mean daily intakes were reported as 1701 mg for men (243% of the RDA) and 1179 mg for women (168% of the RDA). The average intake of women in the lowest quartile of phosphorus intakes was reported as 671 mg per day, 15% greater than the EAR (Lee and Cho 2015).

It is critical to point out that the phosphorus intake figures in NHANES reports are estimated from nutrient databases**.** Comparison of these nutrient database estimates with direct chemical analyses show significant underestimation of phosphorus intake from processed food containing phosphates, with the analytical results for specific foods being 25% to 70% higher than the estimates (Calvo, Moshfegh, and Tucker 2014; Oenning, Vogel, and Calvo 1988; Sullivan, Leon, and Sehgal 2007; Sherman and Mehta 2009; Benini et al. 2011). The actual total phosphorus intake may be as a much as 1000 mg/day greater than the estimate derived from the nutrient database when foods containing phosphate additives comprise a significant portion of the diet (Uribarri and Calvo 2003).

An analysis of NHANES data found that, after adjusting for demographics, cardiovascular risk factors, kidney function, and energy intake, a higher phosphorus intake was associated with higher all-cause mortality in individuals who consumed more than 1400 mg/day, but at intake levels less than 1400 mg/day, there was no association (Chang et al. 2014). Analysis of the NHANES data for individuals with moderate chronic kidney disease ("CKD") found that high dietary phosphorus intakes were not associated with increased mortality in moderate CKD (Murtaugh et al. 2012).

A higher phosphorus intake was associated with higher calcium intake and was positively associated with bone mineral content in female teenagers, and it was also positively associated with bone mineral content and bone mineral density, as well as reduced risk of osteoporosis, in adults over 20 years of age (Lee and Cho 2015).

Sodium: The Adequate Intake (AI) of sodium for adult (19- 50 year old) men and women is 1.5 g day, and the UL is 2.3 g/day. The mean daily intakes are over 4 g for men and over 3 g for women (Institute of Medicine 2005).

Calcium: The EAR for adult men and women is 800 mg per day. The RDA is 1000 mg/day and the UL is 2500 mg/day (Institute of Medicine 2011). The mean daily intake of calcium was 1157 mg for men and 880 mg for women, 12% less than the RDA but 10% more than the EAR. Mean daily calcium intakes of men and women in the lowest quartiles of calcium intakes were 477 mg and 503 mg, respectively, or 35% lower than the EAR (Lee and Cho 2015).

Magnesium: The EAR for men 19- 30 years old is 330 mg/day, and for men 31-50 years old it is 350 mg/day. The EARs for women these ages are 310 mg/day and 265 mg/day, respectively. The RDA is 400 mg and 420 mg for men and 310 mg and 320 mg for women for the two age brackets. Magnesium ingested as a naturally occurring substance in food has not been demonstrated to exert any ill effects. Thus, the UL for magnesium is established for magnesium supplements, which can cause diarrhea and other gastrointestinal effects at high doses. The UL for adolescents and adults is 350 mg of supplementary magnesium (Institute of Medicine 1997).

Magnesium is the nutrient with the greatest prevalence of usual intakes below the weighted EAR for essential minerals among the U.S. population, ages 4 years and older, considering both the magnesium intake from food (56% below the EAR) and the intake from food plus dietary supplements (53% below the EAR) (FDA 2014).

Magnesium interacts with calcium. Foods and supplements are frequently enriched with calcium. Magnesium inhibits the release of calcium ions from the sarcoplasmic reticulum, blocks the influx of calcium ions into the cell by inactivating the calcium channels in the cell membrane, and competes with calcium ions at binding sites on troponin C and myosin, thereby inhibiting the ability of calcium ions to stimulate myocardial tension (Iseri, Chung, and Tobis 1983; Iseri, Freed, and Bures 1975; Iseri and French 1984). Magnesium, a calcium antagonist, may substitute itself for the calcium ions on hydroxyapatite,

producing more soluble phosphate salts and thus inhibiting bone formation and perhaps aortic valve stenosis (Dritsa et al. 2014). Magnesium deficiency in the face of a normal calcium intake has been documented to lead to soft tissue calcification in animals (Chiemchaisri and Phillips 1963, 1965). The most prominent feature of magnesium deficiency is calcification, predominantly of arteries (Kruse, Orent, and McCollum 1933; Tufts and Greenberg 1938; Seelig 1964). Low serum magnesium and high serum phosphorus and calcium are independently associated with greater risk of incident heart failure (Lutsey, Alonso, Michos, et al. 2014).

Magnesium interacts with potassium. Magnesium is necessary for an enzyme responsible for active transport of potassium (Dorup and Clausen 1993). Magnesium regulates the outward movement of potassium in myocardial cells (Matsuda 1991). Magnesium deficiency causes arrhythmia, which may be related to magnesium's role in maintaining intracellular potassium levels (Institute of Medicine 1997).

Potassium: An AI level has been set for potassium because there are insufficient data to estimate an EAR and RDA. The AI for potassium is 4700 mg/day for all adults. "This level of dietary intake should maintain lower blood pressure levels, reduce the adverse effects of sodium chloride intake on blood pressure, reduce the risk of recurrent kidney stones, and possibly decrease bone loss"((Institute of Medicine 2005). The percentages of American men and women who consume amounts of potassium equal to or greater than the AI were estimated to be less than 10% and 1%, respectively (Institute of Medicine 2005). The mean total daily potassium intake of American adults in NHANES 2003-2006 was 2740 mg, only 58% of the AI (Fulgoni et al. 2011). Furthermore, 0% of the population had a potassium intake as high as the AI (Wallace, McBurney, and Fulgoni 2014). Potassium was identified by the 2010 Dietary Guidelines Advisory Committee as being a nutrient of public health concern (Dietary Guidelines Advisory Committee 2010).

Other considerations: Total dietary intakes reflect the sum of the contributions from food and from dietary supplements. NHANES data indicate that in 2003-2006, 51% of Americans consumed multivitamin and mineral supplements containing nine or more micronutrients (Wallace, McBurney, and Fulgoni 2014). Supplement use is growing. For example, use of supplemental calcium increased from 28% among women aged 60 and over during 1988-1994 to 61% during 2003-2006 (Gahche et al. 2011). Dietary intakes of minerals from food sources were higher for magnesium and potassium in male supplement users than in nonusers. For women, dietary intakes of minerals from food sources were higher for users than for nonusers for each mineral examined except for selenium. Supplements reduce the risk of nutrient intakes below the EAR. Women who used calcium-containing dietary supplements were much more likely to meet the EAR than were nonusers. However, even after considering supplement use, more than 14% of adults had inadequate intakes for calcium and magnesium on the basis of the percentage of adults with usual intakes below the EAR (Bailey et al. 2011).

Analysis of the first NHANES in 1984 revealed that a dietary pattern with low mineral intake, specifically calcium, potassium, and magnesium, was associated with hypertension in American adults. Using more recent survey data from NHANES III and NHANES IV, the validity of this relationship was re-examined. Blood pressure (BP) and nutrient intake data from 10,033 adult participants in NHANES III and 2,311 adults in NHANES IV revealed findings similar to those of the earlier analysis, demonstrating that the association between inadequate mineral consumption and higher BP is valid and has persisted over two decades. Exploring this relationship further by separating untreated hypertensive persons by hypertension type (systolic, diastolic or both), the BP effect of low mineral intake was found to be most pronounced in those with only systolic hypertension. Sodium intake was found to be significantly lower in the systolic hypertension group and significantly higher in the diastolic hypertension group compared with the other groups (Townsend et al. 2005).

Summary: The American diet provides very large amounts of phosphorus and sodium. The published phosphorus content is not based on analysis, so the amount of phosphorus consumed is understated. Half of the adult American population consumes less than the EAR of magnesium and essentially no one nowadays consumes the AI of potassium. A substantial proportion of Americans, almost 40%, consume less than the EAR of calcium (Fulgoni et al. 2011). Thus, the major mineral content of the adult American diet is severely imbalanced.

Health effects of phosphorus provided by phosphate additives versus natural phosphorus in foods

Elevated serum phosphate is a risk factor for certain diseases and disease outcomes. In healthy individuals, higher serum phosphate levels have been associated with greater risk for end-stage renal disease and mortality (Sim et al. 2013; Dominguez et al. 2013), abnormally low blood circulation (Meng et al. 2010), abnormally high arterial stiffness (Ix et al. 2009; Kendrick et al. 2010), increased risk of cardiovascular disease (Dhingra et al. 2007) and twice the risk of developing heart failure (Dhingra et al. 2010). Higher levels of serum phosphorus have also been shown to predict coronary artery disease development and progression (Tuttle and Short 2009).

Sodium and potassium phosphates and sodium acid pyrophosphate are very soluble in water, as shown in Table 3. Consequently, the phosphorus in these additives, commonly referred to as "additive phosphorus," is immediately and completely bioavailable upon consumption. In contrast, the phosphorus naturally present in most foods ("food phosphorous") is much less available, in part due to the physical structure of the food and also because digestion of phosphate complexes may be required before the phosphorus can be absorbed.

The digestibility of phosphorus in various foods has been estimated by *in vitro* studies (Karp, Ekholm, Kemi, Hirvonen, et al. 2012; Karp, Ekholm, Kemi, Itkonen, et al. 2012). Only 6% of the phosphorus in sesame seeds with intact hulls was found to be digestible. In legumes, where much of the phosphorus is present as phytate, the average *in vitro* phosphorus digestibility was 38%. In contrast, the "additive phosphorus" in cola drinks and beer was 87-100% digestible. In cereal products the highest total phosphorus content and digestibility were found in industrial muffins containing "additive phosphorus" in the form of sodium pyrophosphate as a leavening agent.

The effect of phosphate on metabolism has been studied in humans using several biomarkers: the blood level free phosphorus ("serum phosphate"), the amount of phosphorus excreted in the urine, the blood level of parathyroid hormone (PTH), the blood level of serum fibroblast growth factor 23 (FGF-23)[2], and the mathematical product of the blood calcium level and the blood phosphorus level score (Takeda et al. 2014; Kwak et al. 2014; Park et al. 2011).

A study by Gutierrez et al. (2015) showed that phosphate additives are more likely to increase serum phosphate levels than natural phosphate from food. Ten healthy individuals were fed a diet providing approximately 1000 mg/day of phosphorus using foods known to be free of phosphorus additives for one week (low-additive diet), immediately followed by a diet comprising identical food items that contained phosphorus additives (additive-enhanced diet). Feeding the additive-enhanced diet for one week significantly increased serum phosphorus as reflected by an increase in circulating FGF-23 levels (Gutierrez et al. 2015).

Another study showed that high total habitual dietary phosphorus intake adversely affected PTH (Kemi et al. 2009). Healthy premenopausal women aged 31-43 years old kept a 4-day food record for calculation of the natural phosphorus (milk and cheese) intake and the additive phosphorus (processed cheese) intake. Comparing the highest total dietary phosphorus quartile to the lowest, mean serum PTH was higher and mean serum ionized calcium was lower where phosphorus intake was higher. Mean PTH was higher among participants who consumed processed cheese and those who consumed less milk and cheese other than processed cheese. Phosphate additives were more harmful to bone than other phosphorus sources, as indicated by higher PTH concentrations (Kemi et al. 2009).

However, a high dietary intake of phosphorus does not always lead to a high serum phosphate level or the associated negative health effects. According to deBoer, Rue and Kestenbaum (2009), dietary intake of phosphorus additives and phosphorus-rich foods are only weakly associated, if at all, with circulating serum phosphorus concentrations, and higher serum phosphorus levels are associated with lower coronary

[2] FGF-23 is a newly discovered growth factor that acts on the parathyroid gland to decrease PTH (parathyroid hormone) mRNA (messenger RNA) and thus reduces PTH secretion in animals with normal kidney function.

heart disease risk scores. In healthy Korean men, neither dietary calcium nor phosphorus intake was consistently associated with coronary artery calcification (CAC) scores. On the other hand, the CAC scores were significantly associated with the blood calcium levels, blood phosphorus levels, and the mathematical product of the blood calcium and phosphorus levels (Kwak et al. 2014; Park et al. 2011). A similar correlation of the serum calcium-phosphorus product with CAC score was reported in individuals with metabolic syndrome (Kim, Lee, and Youn 2013).

One study associated higher FGF-23 levels with higher risks of incident coronary heart disease, heart failure, and cardiovascular mortality (Lutsey, Alonso, Selvin, et al. 2014). The study evaluated the independent association of baseline serum active FGF-23 with incident outcomes involving 11,638 study participants over time. This association was independent of traditional cardiovascular risk factors and kidney function (Lutsey, Alonso, Selvin, et al. 2014).

Serum calcium and phosphorus interact with PTH and FGF-23 to maintain a balance under normal conditions. However, when healthy individuals habitually consume a high phosphorus diet containing insufficient calcium intake, the body compensates to maintain a normal blood calcium level, and bone health is adversely affected (Takeda et al. 2014; Brown and Razzaque 2015). An adequate dietary intake of calcium is needed to overcome the adverse effects of a high phosphorus intake on PTH and FGF-23 secretion. Calcium supplements, providing as little as 100 mg, can reduce serum PTH concentrations and bone resorption (Karp, Ketola, and Lamberg-Allardt 2009).

Increasing dietary calcium to offset high intakes of phosphate impacts the need for other nutrients, particularly magnesium. The magnesium requirements of experimental animals can be doubled by increasing the dietary levels of calcium and phosphorus (Morris and O'Dell 1963). Magnesium deficiency in the face of normal calcium intake has been documented to lead to soft tissue calcification in animals (Chiemchaisri and Phillips 1963, 1965), and a prominent feature of magnesium deficiency is arterial calcification (Kruse, Orent, and McCollum 1933; Tufts and Greenberg 1938; Seelig 1964). Low magnesium status increases serum PTH levels (Paunier 1992). Only about half of American adults consume an adequate amount of magnesium (Rosanoff, Dai, and Shapses 2016).

Summary: The phosphate in phosphate additives is highly bioavailable and more potent for increasing blood phosphate levels than natural phosphate from food. High blood phosphate levels are associated with kidney and vascular disease. A sufficiently high intake of calcium appears to counteract some of the ill effects of excess dietary phosphorus but leads to an increased requirement for magnesium.

Phosphate in organic foods

Due to the restrictions on phosphate use in organic foods, it would be expected that basing a diet on organic foods would reduce the phosphorus intake. De Lorenzo et al. (2010) compared those who ate an "Italian Mediterranean Organic Diet" to participants who followed a similar diet with phosphate additives and found reduced serum homocysteine and phosphorus levels, reduced microalbuminuria, and reduced cardiovascular disease risk in healthy individuals and in those with CKD. The results of this European trial cannot be extrapolated to the U.S. without some reservations. The EU organic regulations allow addition of only one phosphate, monocalcium phosphate, which can only be used as a leavening agent, whereas USDA organic regulations allow sodium pyrophosphate for this purpose and several other phosphates for other uses. These differences could be important, since Karp et al. (Karp, Ekholm, Kemi, Itkonen, et al. 2012) found that the conventional cereal product with the highest total phosphate content (216 mg/100 g), all of which was digestible, was industrial muffins that contained sodium acid pyrophosphate as the leavening agent.

A survey and sampling of grocery stores in the Cleveland, Ohio, area found that 44% of the best-selling grocery items contained phosphorus additives. The additives were particularly common in prepared frozen foods (72%), dry food mixes (70%), packaged meat (65%), bread and baked goods (57%), soup (54%), and yogurt (51%) categories. Some of the comparative non-additive products were "organic," e.g., Kraft Macaroni & Cheese Dinner™ with added phosphate versus Kraft Organic Cheddar Macaroni & Cheese

Dinner™ without added phosphate. Phosphorus additive-containing foods averaged 67 mg phosphorus per 100 g more than matched non-additive containing foods. Sample meals comprised mostly of phosphorus additive-containing foods had 736 mg more phosphorus per day compared to meals consisting only of additive-free foods. Phosphorus additive-free meals cost an average of $2.00 more per day (Leon, Sullivan, and Sehgal 2013).

Evaluation Question #11: Describe any alternative practices that would make the use of any of the petitioned substances unnecessary (7 U.S.C. § 6518 (m) (6)).

Anticaking Agent and Free-Flow Agent: Dicalcium phosphate is used as the diluent of many Vitamin B12 preparations. Other diluents are inert sugar alcohols such as mannitol, or combinations of dicalcium phosphate with microcrystalline cellulose.

pH Control, Buffering: Citrate salts and phosphate salts are effective buffering agents and metal chelators in food systems. They can replace each other in some applications.

Non-Yeast Leavening: Yeast has been used to leaven baked goods since time immemorial. However, yeast-leavened baked goods have a different physical texture and require more time than chemically-leavened foods. Chemical leavening is used instead of yeast for products where fermentation flavors would be undesirable (Matz 1992), or where the batter lacks the elastic structure to hold gas bubbles for more than a few minutes (McGee 2004), or for convenience. For these reasons, muffins, tea breads, scones, pancakes, cakes and cookies could not practically be made without chemical leavening.

Milk Protein Stabilization: Potassium and sodium citrates can replace sodium phosphates and dipotassium phosphate as stabilizers in several dairy food applications. Section 21 CFR 133.173, "pasteurized process cheese food," includes these three citrates along with sodium phosphates and dipotassium phosphate as acceptable emulsifying agents. Sodium citrate is an alternative to sodium phosphate in condensed, evaporated, and non-fat milk processing (Ellinger 1972), and in processed dairy cheese manufacture (Rippen 1986). Potassium citrate and sodium citrate are listed at 7 CFR 205.605(b) as allowed for use in organic food with no annotations. Potassium citrate has positive effects on bone, decreasing bone resorption markers and increasing calcium retention (Karp, Ketola, and Lamberg-Allardt 2009), whereas phosphate food additives have adverse effects on bone biomarkers (Kemi et al. 2009; Karp et al. 2007).

Source of Calcium: Given the importance of the calcium-phosphorus ratio in human nutrition, the only food grade additives currently permitted in foods labeled as "organic" that are capable of supplying substantial amounts of both calcium and phosphorus are the calcium phosphates.

Evaluation Question #12: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Anticaking Agent and Free-Flow Agent: Rice hull powder, a natural food form of silica, may be a suitable substitute for tricalcium phosphate and dicalcium phosphate as an anti-caking agent, flavor carrier and flow aid, since it can replace silicon dioxide for such uses (Pierce 2010).

pH Control, Buffering: Cream of tartar is a natural material purified from argol, the crude tartar deposited in wine casks during aging, which has been used in food preparation for centuries (Farmer 1896). Cream of tartar is identified chemically as potassium bitartrate, potassium acid tartrate, or potassium hydrogen tartrate, and is the standard used to standardize buffer solutions (Lingane 1947). However, this substance is classified as synthetic at 7 CFR 205.605(b).

Non-Yeast Leavening: Historically, baking powder used for chemical leavening was a combination of three nonsynthetic substances: baking soda (sodium bicarbonate), cream of tartar (potassium acid tartrate), and cornstarch (Farmer 1896). It is unknown whether this preparation would be suitable in modern baking systems. Baking soda (sodium bicarbonate) can function as the only chemical leavening agent in some cookie recipes.

Milk Protein Stabilization: The mechanism for milk protein stabilization is primarily chelation of free calcium to prevent curdling. The two major edible calcium-chelating anions are phosphate and citrate. Nonsynthetic citric acid is a source of citrate, but adding acid to milk curdles the milk protein, similar to making cottage cheese.

Source of Calcium: Bone meal, oyster shell, and dolomite are natural materials that have been used as human dietary calcium supplements. Bone meal and oyster shell preparations were found to be contaminated with lead and other toxic metals (Whiting 1994), and bone meal is no longer recommended as a calcium source in the human diet. Dolomite also can have high lead levels (Boulos and von Smolinski 1988). Rock phosphate is a natural form of calcium phosphate but it is naturally contaminated with fluoride (Rama Rao and Reddy 2001) and radionuclides (Menzel 1968).

Evaluation Information #13: Provide a list of organic agricultural products that could be alternatives for the petitioned substance (7 CFR § 205.600 (b) (1)).

The phosphates addressed in this report are purified inorganic chemicals; they are not agricultural products, and they are not foods *per se,* so they cannot be made available as organic agricultural products.

Organic yeast is available for use as a leavening agent for traditionally yeast-leavened baked good, but yeast would not satisfy the leavening need for baked goods requiring chemical leavening.

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§ 73.30 Georgia [Amended]

■ 2. Section 73.30 is amended as follows:

* * * * *

R–3004A Fort Gordon, GA [Amended]

Boundaries. Beginning at lat. 33°25′03″N, long. 82°12′15″W;
to lat. 33°23′48″N, long. 82°08′56″W;
to lat. 33°22′20″N, long. 82°08′33″W;
to lat. 33°21′33″N, long. 82°09′10″W;
to lat. 33°20′15″N, long. 82°10′57″W.,
to lat. 33°17′41″N, long. 82°16′11″W;
to lat. 33°18′23″N, long. 82°16′17″W;
to lat. 33°18′22″N, long. 82°16′39″W;
to lat. 33°17′29″N, long. 82°16′52″W;
to lat. 33°16′57″N, long. 82°17′39″W;
to lat. 33°16′56″N, long. 82°18′50″W;
to lat. 33°17′27″N, long. 82°21′19″W;
to lat. 33°17′41″N, long. 82°22′35″W;
to lat. 33°19′26″N, long. 82°22′15″W;
to lat. 33°22′37″N, long. 82°16′58″W;
to lat. 33°23′50″N, long. 82°14′03″W;
to the point of beginning.

Designated Altitudes. Surface to but not including 2,500 feet MSL.

Time of designation. By NOTAM 24 hours in advance.

Controlling agency. FAA, Atlanta ARTCC.

Using agency. U.S. Army, Commanding Officer, Fort Gordon, GA.

Remarks. Aircraft activities must not be conducted on national holidays or from the Sunday prior to the Masters Golf Tournament through the Monday after (and subsequent weather days if required).

R–3004B Fort Gordon, GA [Amended]

Boundaries. Beginning at lat. 33°25′03″N, long. 82°12′15″W;
to lat. 33°23′48″N, long. 82°08′56″W;
to lat. 33°22′20″N, long. 82°08′33″W;
to lat. 33°21′33″N, long. 82°09′10″W;
to lat. 33°20′15″N, long. 82°10′57″W;
to lat. 33°17′41″N, long. 82°16′11″W;
to lat. 33°18′23″N, long. 82°16′17″W;
to lat. 33°18′22″N, long. 82°16′39″W;
to lat. 33°17′29″N, long. 82°16′52″W;
to lat. 33°16′57″N, long. 82°17′39″W;
to lat. 33°16′56″N, long. 82°18′50″W;
to lat. 33°17′27″N, long. 82°21′19″W;
to lat. 33°17′41″N, long. 82°22′35″W;
to lat. 33°19′26″N, long. 82°22′15″W;
to lat. 33°22′37″N, long. 82°16′58″W;
to lat. 33°23′50″N, long. 82°14′03″W;
to the point of beginning.

Designated Altitudes. 2,500 feet MSL to but not including 10,000 feet MSL.

Time of designation. By NOTAM 24 hours in advance.

Controlling agency. FAA, Atlanta ARTCC.

Using agency. U.S. Army, Commanding Officer, Fort Gordon, GA.

Remarks. Aircraft activities must not be conducted on national holidays or from the Sunday prior to the Masters Golf Tournament through the Monday after (and subsequent weather days if required).

R–3004C Fort Gordon, GA [Amended]

Boundaries. Beginning at lat. 33°25′03″N, long. 82°12′15″W;
to lat. 33°23′48″N, long. 82°08′56″W;
to lat. 33°22′20″N, long. 82°08′33″W;
to lat. 33°21′33″N, long. 82°09′10″W;
to lat. 33°20′15″N, long. 82°10′57″W;
to lat. 33°17′41″N, long. 82°16′11″W;
to lat. 33°18′23″N, long. 82°16′17″W;
to lat. 33°18′22″N, long. 82°16′39″W;
to lat. 33°17′29″N, long. 82°16′52″W;
to lat. 33°16′57″N, long. 82°17′39″W;
to lat. 33°16′56″N, long. 82°18′50″W;
to lat. 33°17′27″N, long. 82°21′19″W;
to lat. 33°17′41″N, long. 82°22′35″W;
to lat. 33°19′26″N, long. 82°22′15″W;
to lat. 33°22′37″N, long. 82°16′58″W;
to lat. 33°23′50″N, long. 82°14′03″W;
to the point of beginning.

Designated Altitudes. 10,000 feet MSL to 16,000 feet MSL.

Times of designation. By NOTAM 24 hours in advance.

Controlling agency. FAA, Atlanta ARTCC.

Using agency. U.S. Army, Commanding Officer, Fort Gordon, GA.

Remarks. Aircraft activities must not be conducted on national holidays or from the Sunday prior to the Masters Golf Tournament through the Monday after (and subsequent weather days if required).

* * * * *

Issued in Washington, DC, on April 4, 2023.

Brian Konie,

Acting Manager, Airspace Rules and Regulations Group.

[FR Doc. 2023–07398 Filed 4–7–23; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 130, 131, 133, 136, 137, 139, 145, 150, 155, 156, 158, 161, 163, 166, 168, and 169

[Docket No. FDA–2022–N–2226]

RIN 0910–AI72

Use of Salt Substitutes To Reduce the Sodium Content in Standardized Foods

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA or we) is proposing to amend our standard of identity (SOI) regulations that specify salt (sodium chloride) as a required or optional ingredient to permit the use of salt substitutes in standardized foods, to reduce the sodium content. Reducing sodium may help reduce the risk of hypertension, a leading cause of heart disease and stroke. The proposed rule, if finalized, would help support a healthier food supply by providing flexibility to facilitate industry innovation in the production of standardized foods lower in sodium while maintaining the basic nature and essential characteristics of the foods.

DATES: Either electronic or written comments on the proposed rule must be submitted by August 8, 2023.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of August 8, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *http://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *http://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand delivery/Courier (for written/paper submissions):* Dockets

Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2022–N–2226 for ''Use of Salt Substitutes to Reduce the Sodium Content in Standardized Foods.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *http://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *http://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Andrew Yeung, Center for Food Safety and Applied Nutrition (HFS–820), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–2371 or Carrol Bascus, Center for Food Safety and Applied Nutrition, Office of Regulations and Policy (HFS–024), Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240–402–2378.

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I. Executive Summary

A. Purpose of the Proposed Rule

This proposed rule, if finalized, would amend FDA's definitions and standards of identity (SOI; the acronym is used to refer to both the singular ''standard of identity'' and the plural ''standards of identity'') that specify salt (sodium chloride) as a required or optional ingredient. Foods for which FDA has established a SOI are referred to as ''standardized'' foods. The amendments would permit the use of safe and suitable salt substitutes to replace some or all of the salt used in the manufacture of standardized foods. The proposed rule would not list specific salt substitutes; instead, the proposed rule would cover ingredients or combinations of ingredients used as salt substitutes by food manufacturers currently or in the future. If finalized, the proposed rule would support efforts to reduce sodium content in standardized foods and may help to improve consumer dietary patterns by reducing sodium consumption. On average Americans consume 50% more sodium than the recommended limit for those aged 14 and older (Ref. 1). Reducing sodium consumption may help reduce the risk of hypertension, a leading cause of heart disease and stroke. The proposed rule would allow food manufacturers the flexibility to use salt substitutes and allow for innovation in producing healthier standardized foods. The proposed rule would promote honesty and fair dealing in the interest of consumers by accommodating their preferences for lower sodium varieties of foods. This, in turn, would make lower-sodium options available to them.

B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to amend its SOI that specify salt as a required or optional ingredient to permit the use of safe and suitable salt substitutes in standardized foods, to reduce the sodium content. We propose to amend our regulation entitled ''Food Standards: General'' (21 CFR part 130) to create a new subpart C entitled ''Flexibility in Standardized Foods'' and add a new section entitled ''Ingredient Flexibility in Standardized Foods'' to define salt substitute. We also propose to amend 80 SOI to permit salt substitutes.

We also propose to update the incorporation by reference (IBR) information of several SOI to refer to the most recent versions of the IBR materials and to provide up-to-date contact information for obtaining the IBR materials. For example, the proposed rule would update the referenced methods of analysis to those in the ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 21st Ed. 2019. We also propose to make technical amendments to correct inconsistencies and typographical errors in some SOI regulations.

We tentatively conclude that the proposed amendments are necessary to modernize SOI to provide flexibility and facilitate innovation in the production of standardized foods with less sodium, and to promote honesty and fair dealing in the interest of consumers.

C. Legal Authority

We are proposing this rule consistent with our authority in sections 201, 401, 402, 409, and 701 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 321, 341, 342, 348, 371). We

discuss our legal authority in greater detail in section IV.

D. Costs and Benefits

The proposed rule would amend SOI that specify salt as a required or optional ingredient, to permit the use of salt substitutes. The proposed rule would give manufacturers the flexibility to use salt substitutes in standardized foods, to reduce sodium content. If finalized, the proposed rule would not result in regulatory costs for firms. The proposal would not require manufacturers to replace salt with salt substitutes. Instead, manufacturers would have the option of using salt substitutes to replace salt in standardized foods. Should manufacturers choose to use this flexibility to reformulate some products by substituting some salt with salt substitutes, the primary benefits realized would result from lower sodium consumption by U.S. consumers who choose to purchase and consume the reformulated versions of such products, and increased profit (producer surplus) for manufacturers (or at least no decrease in profits). The primary cost of such voluntary market behavior would include reformulation and relabeling costs for the manufacturers.

II. Table of Abbreviations/Acronyms

Abbreviation/ acronym	What it means
CDRR	Chronic Disease Risk Reduction Intake
CFR	Code of Federal Regulations
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
FR	FEDERAL REGISTER
GRAS	Generally Recognized as Safe
IBR	Incorporation by Reference
mg	Milligram
SOI	Standard(s) of Identity
U.S.C.	United States Code

III. Background

A. Introduction

As a public health agency, FDA seeks to improve dietary patterns in the United States to help reduce the burden of diet-related chronic diseases and advance health equity as nutrition-related chronic diseases are experienced disproportionately by certain racial and ethnic minority groups, those living in rural communities, and those with lower socioeconomic status. We are committed to accomplishing this, in part, by creating a healthier food supply for all. One way FDA is working towards this goal is by helping to reduce sodium across the food supply.

Americans consume, on average, 3,400 milligrams of sodium per day (mg/day) (Ref. 1). This is nearly 50 percent more than the sodium Chronic Disease Risk Reduction Intake (CDRR) established by the National Academies of Sciences, Engineering and Medicine, which sets the limit for sodium for individuals 14 years and older at 2,300 mg/day. This CDRR was adopted as a recommendation by the Dietary Guidelines for Americans, 2020–2025 (Refs. 1 and 2). Reducing sodium intake to below the CDRR level is expected to help reduce the risk of chronic disease. Excess sodium intake increases risk for hypertension, commonly referred to as high blood pressure, a leading cause of heart disease and stroke and the first and fifth leading cause of mortality in 2020 in the United States (Refs. 2–6). Decreasing sodium intake is, therefore, expected to reduce the rate of hypertension. It has been estimated that sufficient reductions in the population average sodium intake could potentially result in tens of thousands fewer cases of heart disease and stroke and associated mortality each year (Refs. 7–9).

Reducing sodium in processed, packaged and prepared foods will help create a healthier food supply. A healthier food supply has the potential to contribute to better health outcomes and reduce preventable death and disease related to poor nutrition; many of which are experienced at higher rates by certain racial and ethnic groups (Ref. 10). For example, more than 4 in 10 American adults have hypertension and that number increases to nearly 6 in 10 for non-Hispanic Black Americans (Ref. 11). African American women are almost 60 percent more likely to have hypertension when compared to non-Hispanic white women, and African American adults are 30% more likely than non-Hispanic white Americans to die from coronary heart disease (CHD) (Refs. 12 and 13); further, American Indians/Alaskan Natives are 50% more like to be diagnosed with CHD than non-Hispanic Whites (Ref. 13). The proposed rule's likely effect on increasing the availability of lower sodium products may contribute to government-wide efforts to reduce health disparities.

Reducing sodium in processed, packaged and prepared food is a critical step in helping to improve consumer dietary patterns. More than 70 percent of sodium consumed in the United States comes from sodium added during manufacturing and commercial food preparation (Ref. 14). This makes it challenging for consumers to reduce their sodium consumption. Further, because salt (sodium chloride) serves various functions in processed, packaged, and prepared foods, industry must balance sodium reduction efforts while manufacturing products that maintain the properties of a certain food and still meet the preferences of consumers.

FDA is engaged in several efforts aimed at encouraging gradual, efficient reduction of overall sodium content in processed, packaged and prepared food products. We recently issued two guidance documents for industry to support voluntary industry efforts to reduce sodium in the food supply and facilitate industry innovation toward creating healthier foods. The December 2020 guidance for industry entitled ''The Use of an Alternate Name for Potassium Chloride in Food Labeling'' (Potassium Chloride guidance) (Ref. 15) sets forth FDA's enforcement discretion policy with respect to declaring potassium chloride as ''potassium salt'' in the ingredient statement in the labeling of food products. In October 2021, we issued guidance for industry entitled ''Voluntary Sodium Reduction Goals: Target Mean and Upper Bound Concentrations for Sodium in Commercially Processed, Packaged, and Prepared Foods'' (Voluntary Sodium Reduction Goals guidance) (Ref. 16). The guidance document finalizes the short-term (2.5 year) voluntary sodium reduction targets in over 160 categories of packaged and restaurant prepared food. These short-term targets are based on a reduction of average sodium intake from current levels of 3,400 mg/day to 3,000 mg/day, and they serve as initial benchmarks for a broad and gradual reduction of sodium in the food supply (Ref. 16 and 17). Through the two guidance documents and this rulemaking, our intent is to support the gradual reduction of sodium across the food supply.

Under our authority in section 401 of the FD&C Act, FDA establishes SOI to promote honesty and fair dealing in the interest of consumers. SOI are established under the common or usual name of a food. Such foods are said to be ''standardized.'' SOI define the food and typically provide the types of ingredients that it must contain (*i.e.,* mandatory ingredients) and that it may contain (*i.e.,* optional ingredients). They sometimes specify the amount or proportion of each ingredient. Many SOI also designate methods of production. We have over 250 SOI for a wide variety of food products.

B. Need for the Regulation

Salt substitutes are ingredients that can help reduce sodium in processed, packaged and prepared foods. Food manufacturers wishing to reduce salt in their products to accommodate consumer preferences or for other reasons sometimes use substitute ingredients that provide similar taste and other technical functions of salt in foods. Most of our SOI that include salt as a required or optional ingredient do not permit the use of salt substitutes. Therefore, food manufacturers are currently precluded from using salt substitutes in the production of these standardized foods. However, manufacturers may use salt substitutes in the production of non-standardized foods. Various stakeholders have expressed concern that many SOI are out of date and may impede innovation, including the ability to produce healthier foods (Ref. 18). Manufacturers seeking to reduce sodium in standardized foods are limited because they are unable to produce foods using salt substitutes and still conform to the SOI. In this way, the SOI may become a barrier to innovation.

Permitting the use of salt substitutes is aligned with FDA's goal to reduce sodium across the food supply and our work to reduce sodium consumption. Research suggests that consumers usually do not notice small reductions in sodium and, over time, consumer palates adjust to lower sodium levels (Ref. 19). Through our work on the Voluntary Sodium Reduction Goals guidance and the Potassium Chloride guidance, we learned that stakeholders, including industry, consumers, consumer advocacy, scientific and professional health organizations, generally support allowing the use of salt substitutes. In another public engagement, some stakeholders discussed modernizing SOI to allow the use of salt substitutes using a ''horizontal approach'' (Ref. 18). A horizontal approach to amending standards is a change that could be made across all, or broad categories of SOI to provide flexibility and facilitate innovation in the production of more nutritious foods. We considered several options for permitting salt substitutes in standardized foods and evaluated how to apply this change across multiple SOI. The proposed rule, if finalized, would adopt a horizontal approach to amending the applicable SOI. The proposed rule would permit the use of salt substitutes in SOI that specify salt as a required or optional ingredient, to reduce sodium in the food. Because the use of salt substitutes in these SOI is currently precluded, any use of salt substitutes by manufacturers under the rule would contribute to reduced sodium intake to some degree.

Permitting the use of salt substitutes in standardized foods would contribute to our goal to reduce sodium across the food supply. It would facilitate voluntary industry efforts toward sodium reduction by providing flexibility and supporting innovation in the production of healthier standardized foods, which may help some consumers to gradually reduce the sodium in their diet and contribute to better health outcomes. The proposed rule may have the potential to contribute to government-wide efforts to reduce health disparities if the use of salt substitutes helps populations disproportionately affected by hypertension to consume less sodium.

C. FDA's Current Regulatory Framework

The FD&C Act gives us the authority to establish definitions and standards for foods with respect to identity, quality, and fill of container (21 U.S.C. 341). SOI specify the permitted ingredients, both mandatory and optional, and sometimes describe the amount or proportion of each ingredient. Many SOI also prescribe a method of production or formulation. Foods for which FDA has established a SOI must conform to the applicable definition and standard. A food is misbranded if it purports to be or is represented as a food for which a SOI has been established but fails to conform to the definition and standard (21 U.S.C. 343(g)).

SOI are codified in parts 130 to 169 (21 CFR parts 130 to 169). Part 130 outlines general provisions, including the use of food additives in food standards. Part 130 also includes the general definition and SOI (*i.e.,* § 130.10). Parts 131 to 169 set forward SOI for foods in 21 food product categories.

We have long interpreted the term ''salt'' in the food standards in parts 131 to 169 to refer to sodium chloride. Salt is specified as a required or optional ingredient in 80 SOI across these parts. Some SOI cross reference other SOI. For example, in part 136 (21 CFR part 136), salt is an optional ingredient in the SOI for bread, rolls, and buns (§ 136.110) which is referenced in several other SOI, including: enriched bread, rolls, and buns (§ 136.115), milk bread, rolls, and buns (§ 136.130), raisin bread, rolls, and buns (§ 136.160), and whole wheat bread, rolls, and buns (§ 136.180). The result of such cross referencing is that salt is a required or an optional ingredient in 140 SOI.

Manufacturers of standardized foods have few options for reducing the sodium content of their products. If salt is a required ingredient, they may generally use less salt. If salt is an optional ingredient, they may either use no salt or less salt. However, they cannot replace salt with another ingredient unless the standard permits the use of another ingredient. Most SOI do not provide for a substitute for salt. In some instances, we established separate SOI for low sodium foods, thereby allowing manufacturers to reduce the amount of salt used and to substitute other ingredients. Manufacturers may also modify the sodium content of standardized foods under the general definition and SOI in § 130.10 (Requirements for foods named by use of a nutrient content claim and a standardized item), provided that certain conditions are met.

Deviation from a SOI is permitted under the general definition and SOI in § 130.10. The deviation must be due to a modification described by an expressed nutrient content claim defined by regulation. Expressed nutrient content claims for the sodium content of foods (*e.g.,* ''low sodium'') are provided under § 101.61 (21 CFR 101.61) (Nutrient content claims for the sodium content of foods). Thus, sodium modifications to a standardized food are permitted if the modification meets the requirements for a nutrient content claim under § 101.61. The modified food becomes a new standardized food under § 130.10 and is named with the nutrient content claim and the name of the standardized food from which it deviates (*e.g.,* ''low sodium provolone cheese''). It may be impracticable for manufacturers to reduce the sodium content in standardized foods to the extent required by a nutrient content claim. For example, to meet the requirements for a ''reduced sodium'' nutrient content claim, manufacturers must decrease the sodium in the food by at least 25 percent. Certain foods do not retain the same characteristics when the amount of sodium is reduced to this degree, and therefore, the general definition and SOI does not facilitate the production of lower sodium varieties. This proposed rule would allow manufacturers to reduce the sodium in standardized foods in amounts less than the amounts prescribed in § 101.61. This would provide manufacturers greater flexibility when reformulating standardized foods to lower the sodium content.

Presently, three SOI specifically permit the use of a salt substitute. The SOI for low sodium cheddar cheese (§ 133.116) and low sodium colby

cheese (§ 133.121) permit the use of a salt substitute. The SOI for low sodium colby cheese prohibits the use of salt and permits the use of a salt substitute that contains no sodium (§ 133.121(a)). The SOI for margarine (§ 166.110) specifically permits the use of potassium chloride in the manufacture of dietary margarine. Potassium chloride, in some instances, can be used as a partial substitute for sodium chloride in food processing and manufacturing.

If finalized, the proposed rule would provide a new means for manufacturers to reduce the sodium content of standardized foods. Salt substitutes would be permitted in any food for which an SOI has been established and that specifies salt as a required or an optional ingredient. This would be achieved without requiring the minimum reductions in sodium content under § 101.61 and renaming of food products as is required for modifications under § 130.10.

IV. Legal Authority

We are issuing this proposed rule consistent with our authority in sections 201, 401, 402, 409, and 701of the FD&C Act. Section 401 of the FD&C Act directs the Secretary of Health and Human Services (Secretary) to issue regulations fixing and establishing for any food a reasonable definition and standard of identity, standard of quality, or standard of fill of container, whenever in the judgment of the Secretary, such action will promote honesty and fair dealing in the interest of consumers. We tentatively conclude that permitting the use of salt substitutes to replace some or all of the salt used in the production of standardized foods would promote honesty and fair dealing in the interest of consumers. Consumers desire more nutritious and healthy food options, such as lower sodium versions of foods. This proposed rule, if finalized, would allow for industry development and sale of such foods while ensuring that standardized foods meet consumer expectations and preferences with respect to lower-sodium varieties.

FDA has codified food standards in parts 130 to 169. These regulations do not provide either an authorization or exemption from regulation as a food additive under section 409 of the FD&C Act. The FD&C Act defines ''food additive,'' in relevant part, as any substance, the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component of food, if such substance is not generally recognized by experts as safe under the conditions of its intended use (section 201(s) of the FD&C Act). The definition of ''food additive'' exempts any uses that are the subject of prior sanction (section 201(s)(4) of the FD&C Act)). Food additives are deemed unsafe except to the extent that FDA approves their use (section 409(a) of the FD&C Act). Food is adulterated when it contains an unapproved food additive (section 402(a)(2)(C) of the FD&C Act).

We also are issuing this proposed rule under section 701(a) of the FD&C Act, which authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. Regulations issued under section 701(a) ''must effectuate a congressional objective expressed elsewhere in the Act'' (*Association of American Physicians and Surgeons, Inc.* v. *FDA,* 226 F. Supp. 2d 204 (D.D.C. 2002) (citing *Pharm. Mfrs. Ass'n.* v. *FDA,* 484 F. Supp. 1179, 1183 (D. Del. 1980))). Amending SOI to permit the use of salt substitutes would effectuate the congressional objective ''to promote honesty and fair dealing in the interest of consumers'' expressed in section 401 of the FD&C Act. Permitting salt substitutes in standardized foods under this rule may help provide more options to consumers while ensuring that the foods maintain their basic nature and essential characteristics. The proposed amendments to the SOI for dairy products under parts 131, 133, and 135 are issued under section 701(e) of the FD&C Act.

V. Description of the Proposed Rule

The proposed rule, if finalized, would:

- Amend part 130 to add a new subpart C entitled ''Flexibility in Standardized Foods.''
- Add a new § 130.30 to provide for ''Ingredient Flexibility in Standardized Foods'' and define ''salt substitute'' as a safe and suitable ingredient (or combination of ingredients) that is used to replace some or all of the added salt (sodium chloride), to reduce sodium in the food, and that serves the functions of salt in the food.
- Amend the 80 SOI that specify salt as a required or an optional ingredient to add regulatory text to permit the use of salt substitute, as defined in proposed § 130.30.
- Update the IBR information of several SOI to refer to the most recent versions of the IBR materials and to provide up-to-date contact information for obtaining the IBR materials. The proposed rule would also update the referenced methods of analysis to those in the ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 21st Ed. 2019.
- Make technical amendments to correct inconsistencies and typographical errors in some SOI regulations.

A. Scope/Applicability

The proposed rule, if finalized, would amend SOI in parts 131 to 169. Specifically, the proposed rule would permit the use of salt substitutes in the foods covered by 80 SOI that include salt as a required or an optional ingredient. The proposal would also permit the use of salt substitutes in foods covered by SOI that reference some of the 80 SOI.

This rule does not propose to amend the SOI for oysters (§ 161.130). The SOI in § 161.130 provides for the optional use of salt water in the shucking of oysters. We understand that it is not standard industry practice to constitute a salt and water solution for this process. Rather, seawater accessible at the processing location is collected and used in the shucking process. Because salt is not an ingredient added by the manufacturer, we are not proposing to amend this SOI. We request comments on this approach and our understanding of current industry practice.

B. The Basic Nature and Essential Characteristics of a Standardized Food

Proposed § 130.30(b) would require that ingredients used as salt substitutes do not change the basic nature and essential characteristics of the standardized food. FDA previously discussed its understanding about the basic nature of a food in a proposed rule entitled ''Food Standards; General Principles and Food Standards Modernization,'' (70 FR 29214, May 20, 2005). The basic nature of a food is generally what the food is. It concerns the general attributes of the product. For example, the basic nature of a particular type of cheese is that it is a milk-derived food of a certain form and consistency. The essential characteristics of a food may contribute to achieving the basic nature of the food, but consumers may not be aware of the essential characteristics. The essential characteristics of a food are those that distinguish a food. Foods may be distinguished by their ingredients, compositional characteristics, physical characteristics, or levels of certain nutrients or the way they are produced—all of which are the essential characteristics of the food. For example, the essential characteristics of a particular type of cheese may include the bacterial culture used, the processing method, or the fat and moisture content that contribute to the unique characteristics of that cheese.

Use of salt substitutes that do not change the basic nature and essential characteristics of the standardized food under this proposed rule is necessary to ensure the availability of foods that promote honesty and fair dealing in the interest of consumers, in accordance with section 401 of the FD&C Act.

C. Definition of Salt Substitute

Under the FD&C Act, any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA unless that substance is excluded from the definition of a food additive. These excluded food substances include substances that are generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use (''generally recognized as safe'' or ''GRAS''), or the substances are prior sanctioned and excepted from the definition of a food additive. FDA considers salt a common food ingredient that is GRAS for its intended use (21 CFR 182.1(a)). A salt substitute that is added to a standardized food, to replace some or all of the salt, must be an approved food additive or GRAS for its intended use. For example, potassium chloride is a GRAS substance (21 CFR 184.1622).

The proposed rule would amend § 130.30(c)(1) to define salt substitute as a safe and suitable ingredient (see § 130.3(d)) or combination of ingredients that is used to replace some or all of the added salt (sodium chloride), to reduce the sodium in the food, and that serves the functions of salt in the food. We are proposing to define salt substitute broadly to provide flexibility and facilitate innovation in the future without the need for additional rulemaking. Thus, the proposed rule would not list specific salt substitutes; instead, the proposed rule would cover ingredients or combinations of ingredients currently used as salt substitutes and ingredients or combinations of ingredients that may be used as salt substitutes in the future, as a result of advances in food science and technological changes.

Salt is a required or optional ingredient in a wide range of standardized foods. The proposed rule also would allow manufacturers the flexibility to explore new ways to replace salt and reduce the sodium content of standardized foods while preserving the basic nature and essential characteristics of the food.

We recognize that salt serves various functions in standardized foods. For example, depending on the food, salt may be important for taste, microbial safety, and other functions. The proposed definition would require that the salt substitute be used to replace some or all of the added salt, to reduce the sodium in the food, and serve the functions of salt in the food. This would ensure that the salt substitute performs a similar function to salt in the standardized food, while helping to reduce the sodium content. The extent to which salt can be replaced depends on the ability of the salt substitute to replicate the functions of salt in the food without compromising the food's safety and nutritional quality. The proposed rule would not establish a minimum replacement level for salt. It would not prescribe the sodium content of the foods or any parameters pertaining to the production of the food. Manufacturers would determine the level of salt replacement appropriate for the particular standardized food.

Our intent is to provide manufacturers flexibility and facilitate sodium reduction across the food supply while not changing the basic nature and essential characteristics or adversely affecting the nutritional quality and safety of standardized foods. To accomplish this, proposed § 130.30(c)(1) would limit the definition of salt substitute and therefore the use of salt substitutes to an ingredient or a combination of ingredients that serve the functions that salt served in the particular standardized food. The ingredient or combination of ingredients may include substances intended to mitigate the impact of removing salt and are needed to maintain the basic nature and essential characteristics of the food.

Some manufacturers are currently using salt substitutes to reduce sodium in foods in the marketplace. Scientific articles and reports have used several examples of salt substitutes when discussing sodium reduction efforts (Ref. 19, 20, 21). The use of potassium chloride is one example of a safe and suitable ingredient discussed in the scientific literature that, in some instances, serves as a partial substitute for sodium chloride in food processing and manufacturing (Ref. 15). Other examples of ingredients listed in the scientific literature include herbs and spices, yeast extracts, monosodium glutamate, amino acids, and dairy extracts (Ref. 19). The food industry is pursuing sodium reduction efforts, including the use of salt substitutes (*e.g.,* in products marketed as ''low'' or ''reduced'' sodium), in a variety of foods, including in canned fish and soups (Ref. 21). We request data and information on the types of salt substitutes currently being used in the U.S. market to support sodium reduction and on potential salt substitutes that may be used as a result of the new flexibility provided in this proposed rule.

D. Amending Standard of Identity Regulations to Permit Salt Substitutes

We propose to amend our regulations to permit the use of salt substitutes in SOI that specify salt as a required or an optional ingredient. Foods for which FDA has established a SOI must conform to the applicable standard. Consequently, without these amendments, most standardized foods cannot be modified to replace salt with salt substitutes unless salt can be reduced in sufficient quantity to meet a nutrient content claim under § 101.61 (see section III.C). As stated previously, amending 80 applicable SOI to permit the use of salt substitutes is necessary to give manufacturers the most flexibility to use salt substitutes in standardized foods. The proposed rule would permit the use of salt, salt substitute or a combination of the two in applicable standardized foods. Salt substitutes used would be declared on the label in accordance with section 403(i)(2) of the FD&C Act.

Where salt is permitted in our SOI, the use is not described uniformly in the provisions of the standards. This is largely due to the standards having been established with different structural formats. The lack of uniformity is also due to the use of salt differing across different standardized foods. In some foods, salt is a mandatory ingredient, and in other foods, salt is an optional ingredient. For some foods, salt is permitted at a specific point in the manufacturing process, whereas salt is permitted in other foods without regard to manufacturing time. These differences mean that different amendatory language in the individual standards is necessary to permit the use of salt substitutes. To address this, we propose four types of revisions to the current regulatory text in the applicable SOI.

In particular, there are differences in how the use of salt is prescribed in certain SOI for cheeses and related cheese products in part 133 (21 CFR part 133). For example, several SOI for cheeses use terms such as ''salted,'' ''salting,'' ''brine,'' or ''salt solution,'' to prescribe the application of salt in the cheesemaking process. For additional clarity, the proposed amendments for cheeses and related cheese products are grouped and discussed separately from other SOI.

There are 4 types of revisions to the applicable SOI in this proposed rule.

The third and fourth types only apply to SOI in part 133.

- Type 1: When the current text of the SOI lists ''salt'' as an optional ingredient, the proposed rule would amend the SOI to state, ''salt or salt substitute.''
- Type 2: When the current text of the SOI provides for the use of ''salt'' in a paragraph, the proposed rule would amend the SOI to state, ''salt or salt substitute.''
- Type 3: When the current text of the SOI uses terms such as ''salted,'' ''salted with dry salt or brine,'' or ''salting,'' to provide for use of salt in the food, but does not specify salt as an ingredient, the proposed rule would amend the optional ingredient list to add ''salt substitute.''
- Type 4: When the current text of the SOI uses terms such as ''salted,'' or ''salted in brine,'' to provide for the use of salt in the food, but does not provide a list of optional ingredients, the proposed rule would amend the SOI to add a paragraph stating that, ''During the cheesemaking process, where the curd is salted, salt substitute may be used.''

We summarize these changes in tables 1 and 2.

1. Amendments to SOI not in Part 133

We propose amendments to permit the use of salt substitutes in 39 SOI for products that are not cheeses or related cheese products prescribed in part 133. The amendments would occur through two types of revisions to the current regulatory text of the applicable SOI.

a. Type 1 revision for SOI not in part 133. Several SOI provide for the addition of salt by listing it as an ingredient (*e.g.,* as an ''optional ingredient,'' ''other optional ingredient,'' or including salt in a list of substances that could be added as a seasoning or flavoring.) We propose to amend these SOI to permit the addition of a salt substitute in addition to, or in place of, salt by replacing ''salt'' with ''salt or salt substitute.'' For example, the SOI for acidified milk (§ 131.111(e)(8)) lists ''salt'' under ''other optional ingredients;'' the proposed rule would replace ''salt'' with ''salt or salt substitute.'' As another example, the SOI for canned tuna (21 CFR 161.190) includes ''salt'' in a list of seasoning or flavoring ingredients (§ 161.190 (a)(6)(i)); the proposed rule would replace ''salt'' with ''salt or salt substitute.''

b. Type 2 revision for SOI not in part 133. Five SOI prescribe the use of salt in paragraphs that describe the food, rather than as part of an ingredient list. We propose to amend these SOI to permit the addition of a salt substitute in addition to, or in place of, salt by replacing ''salt'' with ''salt or salt substitute'' in the regulatory text. For example, the SOI for catsup (21 CFR 155.194) specifies the optional use of salt by stating, ''[t]he food may contain salt''; and the SOI for self-rising flour (21 CFR 137.180) specifies that the food ''is seasoned with salt.'' In both examples, we propose to replace ''salt'' with ''salt or salt substitute.''

Table 1 summarizes the amendments to the SOI for foods other than cheeses and related cheese products. We request comment on whether there would be safety concerns, technical infeasibilities, or other issues that would prevent the use of a salt substitute in any SOI listed in table 1.

TABLE 1—AMENDMENTS TO DEFINITIONS AND STANDARDS OF IDENTITY—FOODS OTHER THAN CHEESES AND RELATED CHEESE PRODUCTS

CFR section	Title	Paragraph	Type of revision
§ 131.111	Acidified milk	(e)(8)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 131.112	Cultured milk	(d)(8)	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 131.160	Sour cream	(b)(5)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 131.162	Acidified sour cream	(b)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 131.170	Eggnog	(e)(2)	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 136.110	Bread, rolls, and buns	(c)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 137.180	Self-rising flour	(a)	Type 2; amends paragraph that describes the food to add salt substitute.
§ 137.270	Self-rising white corn meal	(a)	Type 2; amends paragraph that describes the food to add salt substitute.
§ 139.110	Macaroni products	(a)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 139.150	Noodle products	(a)(2)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 145.110	Canned applesauce	(a)(2)(iii)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 145.130	Canned figs	(a)(5)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 150.110	Fruit butter	(c)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.120	Canned green beans and canned wax beans.	(a)(3)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.130	Canned corn	(a)(3)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.170	Canned peas	(a)(2)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.190	Canned tomatoes	(a)(2)(iv)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.191	Tomato concentrates	(a)(2)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.194	Catsup	(a)(1)(iv)	Type 2; amends paragraph that describes the food to add salt substitute.
§ 155.200	Certain other canned vegetables	(c)(4)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 155.201	Canned mushrooms	(a)(3)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 156.145	Tomato juice	(a)(1)	Type 2; amends paragraph that describes the food to add salt substitute.
§ 158.170	Frozen peas	(a)(1)(iv)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 161.145	Canned oysters	(a)(1)	Type 2; amends paragraph that describes the food to add salt substitute.
§ 161.170	Canned Pacific salmon	(a)(4)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 161.173	Canned wet pack shrimp in transparent or nontransparent containers.	(a)(4)(i)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 161.190	Canned tuna	(a)(6)(i)	Type 1; amends salt in seasoning and flavoring ingredients to add salt substitute.
§ 163.111	Chocolate liquor	(b)(6)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 163.112	Breakfast cocoa	(b)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 163.123	Sweet chocolate	(b)(3)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 163.124	White chocolate	(b)(4)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 163.130	Milk chocolate	(b)(3)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 166.110	Margarine	(b)(2)	Type 1; amends salt in optional ingredients to add salt substitute.

TABLE 1—AMENDMENTS TO DEFINITIONS AND STANDARDS OF IDENTITY—FOODS OTHER THAN CHEESES AND RELATED CHEESE PRODUCTS—Continued

CFR section	Title	Paragraph	Type of revision
§ 168.130	Cane sirup	(b)(1)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 168.140	Maple sirup	(b)(1)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 168.160	Sorghum sirup	(b)(1)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 168.180	Table sirup	(b)(7)	Type 1; amends salt in optional ingredients to add salt substitute.
§ 169.140	Mayonnaise	(d)(1)	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 169.150	Salad dressing	(e)(1)	Type 1; amends salt in other optional ingredients to add salt substitute.

2. Amendments to SOI in Part 133

Type 1 and type 2 amendments are also proposed for certain SOI for cheeses and related cheese products. We propose type 3 and type 4 amendments for the several SOI in part 133 that specify salt as an ingredient, using terms such as ''brine,'' ''salt brine,'' ''salt solution,'' ''salted,'' and ''salting.'' ''Brine,'' ''salt brine,'' and ''salt solution'' are solutions containing sodium chloride and ''salted'' and ''salting'' in the manufacture of cheese refer to the use of sodium chloride. The proposed rule would provide manufacturers of standardized cheeses and related cheese products, the flexibility to use salt substitutes to replace some or all of the salt prescribed in these processes.

We propose to permit the use of salt substitutes in 41 SOI for cheeses and related cheese products. Some SOI in part 133 list salt under ''optional ingredients'' or ''other optional ingredients,'' while others vary in how they prescribe the use of salt in the paragraph that describes the cheese or cheesemaking process. Because of these differences, we propose four types of revisions to the current regulatory text of the applicable SOI for cheeses and related cheese products.

a. Type 1 revision for SOI in part 133. Several SOI for cheeses and related cheese products provide for the addition of salt by listing it as an ingredient (*e.g.,* as an ''optional ingredient'' or ''other optional ingredient.'') We propose to amend these SOI to permit the addition of salt substitute in addition to, or in place of, salt by replacing ''salt'' in the list with ''salt or salt substitute.'' For example, the SOI for cold-pack and club cheese lists ''salt'' under ''optional ingredients'' (§ 133.123(c)(3)). The proposed rule would replace ''salt'' with ''salt or salt substitute.''

b. Type 2 revision for SOI in part 133. Five SOI provide for the use of salt in paragraphs that describe the cheese, rather than as part of an ingredient list. We propose to amend these SOI to permit the addition of a salt substitute in addition to, or in place of, salt by replacing ''salt'' in the paragraphs with ''salt or salt substitute.'' For example, the proposed rule would replace ''salt'' with ''salt or salt substitute'' in three paragraphs of the SOI for dry curd cottage cheese (§ 133.129(b)(1)(i) through (iii)) and in one paragraph of the SOI for sap sago cheese (§ 133.186 (a)(2)).

c. Type 3 revision for SOI in part 133. Some SOI for cheeses and related cheese products provide for the use of salt in a paragraph that describes the cheesemaking process, through terms such as ''salted,'' ''salted with dry salt or brine,'' or ''salting,'' and do not specify salt in a list of ingredients (*e.g.,* as an ''other optional ingredient''). We propose to amend these SOI to permit the addition of a salt substitute in addition to, or in place of, salt by adding ''salt substitute'' as a new subparagraph in the current list of other optional ingredients. For example, the SOI for cheddar cheese (§ 133.113(a)(3)) states that ''the curd is salted, stirred, further drained, and pressed into forms,'' but does not list salt in the optional ingredients in § 133.113(b)(3). The proposed rule would amend § 133.113(b)(3) by adding a new subparagraph, ''salt substitute'' (proposed § 133.113(b)(3)(vi)).

d. Type 4 revision for SOI in part 133. Several SOI for cheeses and related cheese products provide for the use of salt in a paragraph that describes the cheesemaking process through terms such as ''salted'' or ''salted in brine,'' but do not include a list of ingredients (*e.g.,* ''optional ingredient'' or ''other optional ingredient'') that could be amended to add salt substitute. We propose to amend these SOI to explicitly permit the use of a salt substitute in the cheesemaking process. For example, the SOI for asiago fresh and asiago soft cheese (§ 133.102(b)) provides that ''the curd is salted in brine and cured in a well-ventilated room,'' but does not have an optional ingredient list. The proposed rule would amend this SOI by adding a new subparagraph at § 133.102(c)(3) to state, ''During the cheesemaking process, where the curd is salted, salt substitute may be used.''

Table 2 summarizes the amendments to the SOI for cheeses and related cheese products. We request comment on whether there would be safety concerns, technical infeasibilities, or other issues that would prevent the use of salt substitute in any SOI listed in table 2.

TABLE 2—PROPOSED AMENDMENTS TO DEFINITIONS AND STANDARDS OF IDENTITY—CHEESES AND RELATED CHEESE PRODUCTS

CFR section	Title	Current paragraph	Revised or added paragraph designation	Type of revision
§ 133.102	Asiago fresh and asiago soft cheese.	(c)	(c)(3)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.106	Blue cheese	(b)(3)	(b)(3)(vii)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.108	Brick cheese	(b)(3)	(b)(3)(v)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.111	Caciocavallo siciliano cheese	(c)	(c)(3)	Type 4; amends SOI to add a new paragraph to permit salt substitute.

TABLE 2—PROPOSED AMENDMENTS TO DEFINITIONS AND STANDARDS OF IDENTITY—CHEESES AND RELATED CHEESE PRODUCTS—Continued

CFR section	Title	Current paragraph	Revised or added paragraph designation	Type of revision
§ 133.113	Cheddar cheese	(b)(3)	(b)(3)(vi)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.118	Colby cheese	(c)	(c)(4)	Type 4; amends SOI to add new paragraph to permit salt substitute.
§ 133.123	Cold-pack and club cheese	(c)(3)	N/A	Type 1; amends salt in optional ingredients to add salt substitute.
§ 133.124	Cold-pack cheese food	(e)(3)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.127	Cook cheese, koch kaese	(b)(3)(v)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.129	Dry curd cottage cheese	(b)(1)(i)–(iii)	N/A	Type 2; amends paragraph that describes the food to add salt substitute.
§ 133.133	Cream cheese	(b)(3)(i)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.136	Washed curd and soaked curd cheese.	(b)(3)	(b)(3)(vi)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.138	Edam cheese	(b)(3)	(b)(3)(v)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.141	Gorgonzola cheese	(b)(3)	(b)(3)(vii)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.144	Granular and stirred curd cheese.	(b)(3)	(b)(3)(vi)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.
§ 133.147	Grated American cheese food	(c)(5)	N/A	Type 1; amend salt in other optional ingredients to add salt substitute.
§ 133.148	Hard grating cheeses	(c)	(c)(1) and (2)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.149	Gruyere cheese	(b)(3)	(b)(3)(iv)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.
§ 133.150	Hard cheeses	(c)	(c)(3)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.152	Limburger cheese	(b)(3)	(b)(3)(iv)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.153	Monterey cheese and monterey jack cheese.	(b)(3)(iii)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.155	Mozzarella cheese and scamorza cheese.	(b)(3)(iii)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.156	Low-moisture mozzarella and scamorza cheese.	(b)(3)(iii)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.160	Muenster and munster cheese.	(b)(3)	(b)(3)(vi)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.
§ 133.162	Neufchatel cheese	(b)(3)(i)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.164	Nuworld cheese	(b)(3)	(b)(3)(iv)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.
§ 133.165	Parmesan and reggiano cheese.	(c)	(c)(3)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.169	Pasteurized process cheese	(d)(4)	N/A	Type 1; amends salt in optional ingredients to add salt substitute.
§ 133.173	Pasteurized process cheese food.	(e)(4) Salt	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.179	Pasteurized process cheese spread.	(f)(5) Salt	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.181	Provolone cheese	(b)(3)	(b)(3)(vi)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.
§ 133.182	Soft ripened cheeses	(b)	N/A	Type 2; amends paragraph that describes the food to add salt substitute.
§ 133.183	Romano cheese	(c)	(c)(3)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.184	Roquefort cheese, sheep's milk blue-mold, and blue-mold cheese from sheep's milk.	(b)(3)	(b)(3)(i) and (ii)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.185	Samsoe cheese	(b)(3)	(b)(3)(v)	Type 3; amends other optional ingredients to add new paragraph to list salt substitute.
§ 133.186	Sap sago cheese	(a)	N/A	Type 2; amends paragraph that describes the food to add salt substitute.
§ 133.187	Semisoft cheeses	(b)	N/A	Type 2; amends paragraph that describes the food to add salt substitute.

TABLE 2—PROPOSED AMENDMENTS TO DEFINITIONS AND STANDARDS OF IDENTITY—CHEESES AND RELATED CHEESE PRODUCTS—Continued

CFR section	Title	Current paragraph	Revised or added paragraph designation	Type of revision
§ 133.188	Semisoft part-skim cheeses	(b)	N/A	Type 2; amends paragraph that describes the food to add salt substitute.
§ 133.189	Skim milk cheese for manufacturing.	(d)	(d)(1) and (2)	Type 4; amends SOI to add a new paragraph to permit salt substitute.
§ 133.190	Spiced cheeses	(b)(3)(iii)	N/A	Type 1; amends salt in other optional ingredients to add salt substitute.
§ 133.195	Swiss and emmentaler cheese.	(b)(3)	(b)(3)(vii)	Type 3; amends other optional ingredients to add a new paragraph to list salt substitute.

E. Update Incorporation by Reference

Several of the 80 SOI that specify salt as a required or optional ingredient contain outdated references. We propose to update the IBR paragraphs in these SOI to refer to the most recent versions of the IBR materials and to provide up-to-date contact information for obtaining the IBR materials. We propose to add IBR paragraphs to subparts A of parts 131, 137, 139, 150, 155, and 161. SOI in subparts B of these parts would reference applicable IBR paragraphs in subpart A. We also propose to update the IBR paragraphs in the SOI under parts 136, 145, and 166 which would not have IBR paragraphs in subparts A of these parts. The revised format is for administrative efficiency. Specifically, the proposed rule would update the IBR information for §§ 131.111, 131.112, 131.160, 131.162, 131.170, 136.110, 137.180, 137.270, 139.110, 139.150, 145.110, 150.110, 155.120, 155.130, 155.170, 161.145, 161.173,161.190, and 166.110. These SOI list methods of analysis that are from the 13th or 15th editions of ''Official Methods of Analysis of the Association of Official Analytical Chemists.'' Additionally, § 155.170 lists an incorrect section number for the method for alcohol insoluble solids in canned peas. We propose to update the referenced methods of analysis to those in the ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 21st Ed. 2019. These proposed changes will ensure that the reference materials are current, accessible, and meet Federal requirements pertaining to IBR (see 1 CFR part 51).

- Definition of Terms and Explanatory Notes; Table 1. Nominal Dimensions of Standard Test Sieves (USA Standard Series). The reference lists the test sieve designations and their nominal dimensions.
- AOAC Reference Table 909.04; Correction Factors for Gasometric Determination of Carbon Dioxide. The reference lists the correction factors of carbon dioxide measurements for different atmospheric conditions.
- AOAC Official Method 923.02A; Reagent under Carbon Dioxide (Total) in Baking Powders-Gasometric Determination. The reference describes the reagent used in measuring the amount of carbon dioxide released from a sample.
- AOAC Official Method 923.02B; Apparatus under Carbon Dioxide (Total) in Baking Powders-Gasometric Determination. The reference describes the apparatus used in measuring the amount of carbon dioxide released from a sample.
- AOAC Official method 926.07A; Vacuum Oven Method, under Solids (Total) and Loss on Drying (Moisture) in Macaroni Products. The reference provides method references for the preparation of a sample and the total solid determination of a sample.
- AOAC Official method 932.12; Solids (Soluble) in Fruits and Fruit Products. The reference provides a method reference for measuring soluble solids and the formula for calculating the percentage of soluble solids in a sample.
- AOAC Official method 932.14C; By Means of Refractometer under Solids in Syrups. The reference provides the method for measuring the percentage of soluble solids in a sample.
- AOAC Official method 935.36(a); Solids (Total) in Bread. The reference provides the method for measuring the percentage of solids in a sample.
- AOAC Official method 938.06A; Indirect Method, under Fat in Butter. The reference provides the method for measuring the percentage of fat in a sample.
- AOAC Official method 938.10; Solids (Alcohol-Insoluble) in Canned Peas Gravimetric Method. The reference provides the method for measuring the percentage of alcohol-insoluble solids in a sample.
- AOAC Official Method 945.48G; under Evaporated Milk (Unsweetened). The reference provides the method for sample preparation and a method reference for measuring the percentage of milk fat in a sample.
- AOAC Official Method 947.05; Acidity of Milk Titrimetric Method. The reference provides the method for measuring the percentage of lactic acid in a sample.
- AOAC Official Method 989.05; Fat in Milk-Modified Mojonnier Ether Extraction method. The reference provides the method for measuring the percentage of milk fat in a sample.
- AOAC Official Method 990.21; Solid-Not-Fat in Milk By Difference between Total Solids and Fat Contents. The reference provides method references for measuring total solids and fat contents of a sample and the formula for calculating the percentage of nonfat solid in a sample.

You may purchase a copy of the material from AOAC International (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622. You may inspect a copy at Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500, between 9 a.m. and 4 p.m., Monday through Friday.

F. Technical Amendments

We also propose to make technical amendments to correct inconsistencies and typographical errors in several of the 80 SOI regulations that specify salt as a required or optional ingredient. The corrections are non-substantive. The proposed rule would:

- Amend § 133.118(c)(2) to replace ''143'' with ''145.''
- Amend § 133.150(c)(2) to replace ''143'' with ''145.''
- Amend § 133.150(e)(1) to replace ''unusual'' with ''usual.''
- Amend § 133.182(c)(2) to replace ''143'' with ''145.''

- Amend § 133.184(b) to replace ''Operational'' with ''Optional.''
- Amend § 133.186(c) to replace ''Nonmenclature'' with ''Nomenclature.''
- Amend § 133.187(c)(2) to replace ''143'' with ''145.''
- Amend § 133.188(c)(2) to replace ''143'' with ''145.''
- Amend § 155.170(b)(1)(iii) to replace ''shrivelled'' with ''shriveled.''
- Amend § 158.170(b)(1)(iii) to replace ''shrivelled'' with ''shriveled.''
- Amend § 168.140(a) to replace ''mapel'' with ''maple.''

VI. Proposed Effective/Compliance Dates

We propose that any final rule resulting from this rulemaking be effective 30 days after the final rule's date of publication in the **Federal Register** insofar as it amends non-dairy SOI. We believe that this effective date is appropriate because it will provide industry the flexibility to use salt substitutes to reduce the sodium content in standardized foods. Some manufacturers are already exploring ways to reduce sodium in standardized foods, and this proposed rule, if finalized, will assist in those efforts. For the same reasons, FDA proposes that any dairy SOI that may be amended based on this proposal, unless stayed by the filing of proper objections, will also be effective 30 days after the final rule's date of publication in the **Federal Register**.

VII. Preliminary Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Office of Information and Regulatory Affairs has determined that this proposed rule is a significant regulatory action as defined by Executive Order 12866 Section 3(f)(1).[1]

[1] We note that this Executive Order 12866 applies only to the non-dairy SOI portions of this rulemaking; the dairy SOI covered by this rulemaking are ''regulations or rules issued in accordance with the formal rulemaking provisions of 5 U.S.C. 556, 557'' (see 21 U.S.C. 701(e)(1)) and therefore excluded by section (d)(1) of Executive Order (E.O.) 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. We do not anticipate the proposed rule would generate regulatory impacts on small entities. As with any voluntary market behavior, larger firms may have certain advantages over small firms in some areas, while smaller firms may have advantages in other areas. As a result, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $165 million, using the most current (2021) Implicit Price Deflator for the Gross Domestic Product. The proposed rule would not result in a mandated expenditure in any year that meets or exceeds this amount.

The proposed rule would permit, but not require, manufacturers to use salt substitutes to replace salt where salt is a required or optional ingredient in standardized foods. If finalized, the benefits of this rule would be additional flexibility in the manufacture of standardized foods and the potential for reduced salt consumption by consumers which may contribute to better health outcomes. We have no information to suggest the use of currently available salt substitutes would lead to improved product characteristics (*e.g.,* shelf life) or would lead to reduced production costs and potentially lower prices. We request comment on such potential benefits of reformulation for manufacturers and on how many standardized foods manufacturers might choose to reformulate, either in the relatively near or longer-run future.

The proposed rule, if finalized, would not impose requirements resulting in regulatory costs on firms or consumers. Manufacturers would have the *option* of using salt substitutes. There are no regulatory implications for not reading the rule or deciding not to use salt substitutes. Should manufacturers choose to use this flexibility to reformulate some products by substituting some salt with salt substitutes, the primary benefits realized would result from lower sodium consumption on average by U.S. consumers, assuming they choose to purchase and consume the reformulated versions of such products, and increased profit (producer surplus) for manufacturers, assuming they find offering reformulated versions of such products consistent with maximizing firm profits. The primary costs of such voluntary market behavior would be reformulation and relabeling costs for manufacturers. We currently lack data to estimate any net social benefits from voluntary market behavior relating to future use of salt substitutes made possible by this rule, but cite some published analyses below related to meeting voluntary sodium reduction targets that could partially be addressed via the flexibility provided by this rule. We request public comment on possible producer response (*e.g.,* how many manufacturers may choose to take voluntary action in response to this rule, what share of standardized food products may get reformulated) and on possible consumer willingness to purchase and consume such products with various types of salt substitutes at various levels, which would allow us to provide a range of net social benefit estimates when this rule is finalized.

A. Economic Analysis of Impacts

1. Background

There are 80 SOI that specify salt as a mandatory or optional ingredient. Some of these standards are referenced by other SOI, resulting in salt as an ingredient in 140 SOI. The salt in the foods covered by these 140 SOI may serve a variety of functions such as taste, texture, moisture control, and microbial safety. FDA has a public health interest in reducing sodium across the food supply. Therefore, we propose to give manufacturers the flexibility to use salt substitutes in standardized foods where salt is a required or optional ingredient, to reduce the sodium content. While there may be potential data sources (*e.g.,* IRI, Label Insight, Mintel, NHANES, Syndigo) that could provide market or consumption share (*e.g.,* contribution of sodium and/or caloric intake) for foods covered by these 140 SOI, FDA does not currently have sufficient estimates to further extrapolate impacts at this time. We request public comment on additional potential data sources for estimates of market share and/or caloric and/or sodium consumption share of the products included in these SOI.

We request comment on potential regulatory alternatives including allowing the use of only specified salt substitutes, at only specified levels of substitution, for only specified

purposes, for only specified products, in conjunction with only specified ancillary formulation changes, or with specified labeling requirements. More generally, we request comments on potential regulatory approaches to reducing salt in food or the dietary intake of salt that do not involve allowing the use of salt substitutes in standardized foods.

2. Benefits of the Proposed Rule

The benefit of this proposed rule is that manufacturers would have additional flexibility in producing standardized foods covered by 140 SOI, which may lead to social benefits in the form of increased consumer satisfaction (consumer surplus), increased profits (producer surplus), or both. In addition, a change in voluntary market behavior relating to patterns of food consumption, or to use a potassium-based salt as a salt substitute and consumers who would benefit from increasing their potassium intake choose to consume those products, those consumers may experience positive health effects.

Salt is a relatively inexpensive ingredient, and we would not expect manufacturers to begin using salt substitutes based on cost cutting considerations alone at this time. To explore the possibility of manufacturers voluntarily replacing salt with salt substitutes to improve the healthfulness of their standardized foods, one would need to identify the costs and level of potential substitution, and extent of consumer acceptance of salt substitutes at differing levels in different standardized foods in order to estimate the number of manufacturers who would decide to use salt substitutes. We currently lack data on these potential industry responses and request public comment from manufactures, suppliers, and consumers on the extent to which the additional flexibility provided by this rule would be used by manufacturers, hence also desired or tolerated by consumers, and viable in the supply chain.

As discussed in the preamble of this rule, on average, Americans consume approximately 3,400 milligrams of sodium per day (mg/day), which is nearly 50 percent more than the recommended daily limit on sodium intake for individuals 14 years and older (Refs. 1 and 2). Excess sodium intake increases the risk for hypertension, or high blood pressure, a leading cause of heart disease and stroke (Refs. 2–6). Decreasing sodium consumption is expected to reduce hypertension and potentially result in fewer cases of heart disease and stroke (Refs. 7–9 [2]). More than 70 percent of sodium consumed in the U.S. comes from sodium added during manufacturing and commercial food preparation (Ref. 14). The health benefits from reducing sodium consumption are expected to be higher for populations that currently have higher sodium consumption or that are more sensitive to any given level of sodium consumption than other populations. Hence, there may be potential health equity effects to any regulation that generates or facilitates reduced intake of sodium. In order to estimate such health benefits, we would need data and information on the complex pathway between allowing manufactures to use salt substitutes, the extent to which manufactures will develop products of interest to those at highest risk of hypertension, the likely demographic patterns of consumers purchasing those new products, and eventually, the extent of the reduction in sodium uptake among those at most risk of hypertension.

In the absence of necessary data to fully estimate the impacts of this rule, we refer to published literature on the health benefits of sodium reduction targets to provide broader context of potential impacts of this rule. A 2018 study by Pearson-Stuttard, et al. looked at the health and economic effects of FDA's 2016 draft voluntary sodium reduction guidance (Refs. 8 and 22) and estimated benefits of meeting sodium reduction targets in the form of medical cost savings and consumer health improvements, net of producer reformulation costs and some government administrative and monitoring costs. Over a 20-year period, the authors of the study find net social benefits from only consumer health effects to be roughly $12 billion (uncertainty range of $0 billion to $28 billion) under what it described as the most pessimistic scenario relating to potential sodium reduction among the three presented (Ref. 8). This roughly $12 billion *net* benefit arises from roughly $19 billion in estimated health cost savings (benefits) and just over $7 billion of estimated reformulation, administrative and monitoring costs.[3]

Since these benefit estimates are not comprehensive, we would need additional data on possible producer and consumer response to fully assess health benefits. Moreover, benefits might be higher or lower than what would be indicated by estimates that focus on the subset of effects tracked by Pearson-Stuttard et al. Benefits might be higher if firms were to realize additional profits or producer surplus from any product reformulation (since we assume firms would use salt substitutes only if profits would remain the same or increase). Benefits might also be higher due to possible changes in consumer surplus from consumers willing to buy reformulated products whose valuation includes factors beyond medical cost savings or health state utility. Benefits might be lower if some consumers experience disutility associated with the reformulated product and adjust their consumption pattern accordingly, which could partially offset the estimated health benefits presented above.

In addition, as mentioned above, we currently lack data to determine how much, if any, of the aggregate effects that Pearson-Stuttard et al. attribute to broader voluntary sodium reduction efforts could be directly connected to the flexibility provided by this rule. The rule does not cover all foods analyzed in the Pearson-Stuttard, et al. scenarios, which included many non-standardized foods. With comprehensive data on the share of foods affected by this rule, we could estimate health benefits across only such products as a subset of the Pearson-Stuttard, et al. estimate. We request such data and also data on possible consumer and producer response to the flexibility provided by this rule.

3. Costs of the Proposed Rule

The proposed rule, if finalized would not impose *regulatory* costs on manufacturers or consumers. There would be no regulatory requirements or regulatory penalties relative to the baseline of taking no regulatory action. Manufacturers would be required to use safe and suitable ingredients regardless of the amount or type of salt substitutes they choose to use. The flexibility provided by this rule creates parity for use of existing salt substitutes in both standardized and non-standardized foods (see section V.C. for discussion of examples of current salt substitutes in use) and such uses are already required to be disclosed and labeled. It is

[2] These studies may be sensitive to assumptions regarding consumer response. If some consumers experience disutility associated with the reformulated product and adjust their consumption pattern accordingly, this could partially offset some of the estimated health benefits.

[3] These results may be sensitive to assumptions regarding consumer response to product reformulation. For example, benefits might be lower if some consumers experience disutility associated with the reformulated product and adjust their consumption pattern accordingly, which could partially offset the estimated health benefits presented above. Ref. 9, for instance, indicates that its cost-effectiveness results are highly sensitive to such issues.

possible that a change in voluntary market behavior relating to food consumption may generate health costs. For example, to the extent manufacturers choose to use potassium chloride as a salt substitute and consumers choose to consume those products, consumers who may need to limit their potassium intake may see negative health effects that should be accounted for in cost estimates. We request comments on evidence that could contribute to a more thorough assessment (including possible quantification) of such costs. The agency will continue to monitor the use of salt substitutes in the U.S. food supply.

The economic rationale for food standards involves reducing consumers' search costs; in particular, their ability to infer certain product characteristics from representation as certain standardized foods. The proposed rule may affect product characteristics by allowing manufacturers to use salt substitutes that replace any one or any combination of the functions of added salt. However, the proposed rule would preclude ingredient substitutions that change the basic nature and essential characteristics of a standardized food. The basic nature of a food concerns the general attributes of the product that is offered for sale to consumers. The essential characteristics of a food may contribute to achieving the basic nature of the food, but consumers may not be aware of the essential characteristics. Use of safe and suitable salt substitutes that do not change the basic nature and essential characteristics of the standardized food ensures that products on the market retain their general attributes. For purposes of this analysis, we assume products that retain their general attributes will also retain consistency with consumer beliefs and expectations relating to those products and that the use of salt substitutes will therefore not generate consumer dissatisfaction relating to the identity of the standardized food. To the extent that this assumption may not be accurate, we request comment on the degree to which consumers may be willing to purchase and consume such products after salt substitutes are used.

If finalized, manufacturers may choose to take advantage of the flexibility provided in this proposed rule. As discussed above, the primary potential costs of that voluntary market behavior would arise from producers choosing to use the flexibility afforded to them to reformulate some products such as reformulation, consumer testing, labeling, and possibly marketing costs. Pearson-Stuttard, et al., estimate that reformulation costs (using the FDA model, Ref. 23) corresponding to the draft voluntary short term sodium reduction targets could range from $2.7 to $15 billion over a 20-year time period and that these costs would comprise roughly 95 percent of the costs related to reaching short term sodium reduction targets (Ref. 8). Producers may voluntarily choose to reformulate some products in response to this rule's added flexibility and the magnitude of such costs would depend on the number of products reformulated. The more firms choose to reformulate using salt substitutes given the flexibility provided by this rule, the greater the share of sodium reduction efforts (and associated reformulation costs) that could be attributed to this rule. Regardless of what amount of reformulation producers voluntarily choose to undertake, they will only do so if their private benefits in the form of increased revenue are at least as much as their private costs. We request comment on the number of manufacturers who may choose to reformulate standardized food products and the extent to which manufacturers may choose to reformulate those products given this new flexibility. We also request comment on all other considerations relating to manufacturers' voluntary market decision to use salt substitutes including cost of reformulation, ability to source substitute ingredients, expected impact on sales, profits, and consumer acceptance or lack of acceptance.

B. Initial Small Entity Analysis

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. If finalized, we do not expect the proposed rule would generate impacts on small entities. The rule would not impose regulatory costs on small entities. There would be no regulatory requirements or regulatory penalties relative to the baseline of taking no regulatory action. We have no basis to suppose or estimate any other impacts on small entities. As a result, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

This analysis is also available in the docket for this proposed rule (Ref. 24) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.32(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

X. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the rule does not contain policies that would have a substantial direct effect on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes. We invite comments from tribal officials on any potential impact on Indian tribes from this proposed action.

XII. References

The following references marked with an asterisk (*) are on display with the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *http://www.regulations.gov.* References without asterisks are not on public

display at *http://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

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List of Subjects

21 CFR Part 130

Food additives, Food grades and standards.

21 CFR Part 131

Dairy products, Food grades and standards, Incorporation by reference, Milk.

21 CFR Part 133

Dairy products, Food grades and standards, Food labeling.

21 CFR Part 136

Bakery products, Food grades and standards, Incorporation by reference.

21 CFR Part 137

Foods, Food grades and standards, Incorporation by reference.

21 CFR Part 139

Food grades and standards, Incorporation by reference.

21 CFR Parts 145 and 150

Food grades and standards, Fruits, Incorporation by reference.

21 CFR Part 155

Food grades and standards, Incorporation by reference, Vegetables.

21 CFR Part 156

Food grades and standards, Vegetable juices.

21 CFR Part 158

Food grades and standards, Frozen foods, Vegetables.

21 CFR Part 161

Food grades and standards, Frozen foods, Incorporation by reference, Seafood.

21 CFR Part 163

Cacao products, Food grades and standards.

21 CFR Part 166

Food grades and standards, Food labeling, Incorporation by reference, Margarine.

21 CFR Part 168

Food grades and standards, Sugar.

21 CFR Part 169

Food grades and standards, Oils and fats, Spices and flavorings.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR parts 130, 131, 133, 136, 137, 139, 145, 150, 155, 156, 158, 161, 163, 166, 168, and 169 be amended as follows:

PART 130—FOOD STANDARDS: GENERAL

■ 1. The authority citation for part 130 continues to read as follows:

Authority: 21 U.S.C. 321, 336, 341, 343, 371.

■ 2. Add subpart C to read as follows:

* * * * *

Subpart C—Flexibility in Standardized Foods

§ 130.30 Ingredient flexibility in standardized foods.

(a) The definitions listed in this section apply to parts 131 through 169 of this chapter.

(b) The ingredients used as substitutes must not change the basic nature and essential characteristics of the food.

(c) *Definitions.*

(1) Salt substitute means a safe and suitable ingredient (or combination of ingredients) that is used to replace some or all of the added salt (sodium chloride), to reduce sodium in the food, and that serves the functions of salt in the food.

(2) [Reserved]

PART 131—MILK AND CREAM

■ 3. The authority citation for part 131 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 4. Add § 131.10 to read as follows:

§ 131.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622:

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) AOAC Official Method 945.48G, under Evaporated Milk (Unsweetened); IBR §§ 131.160(c); 131.162(c).

(2) AOAC Official Method 947.05, Acidity of Milk Titrimetric Method; IBR §§ 131.111(f); 131.112(e); 131.160(c); 131.162(c).

(3) AOAC Official Method 989.05, Fat in Milk Modified Mojonnier Ether Extraction Method; IBR §§ 131.111(f); 131.112(e); 131.170(f).

(4) AOAC Official Method 990.21, Solid-Not-Fat in Milk By Difference between Total Solids and Fat Contents; IBR §§ 131.111(f); 131.112(e); 131.170(f).

(b) [Reserved]

■ 5. In § 131.111, revise paragraphs (e)(8) and (f) to read as follows:

§ 131.111 Acidified milk.

* * * * *

(e) * * *

(8) Salt or salt substitute.

* * * * *

(f) *Methods of analysis.* Referenced methods are from ''Official Methods of Analysis'' (incorporated by reference, see § 131.10):

(1) Milkfat content—As determined by the method prescribed in AOAC Official Method 989.05, Fat in Milk Modified Mojonnier Ether Extraction Method.

(2) Milk solids not fat content—Calculated by subtracting the milkfat content from the total solids content using the method prescribed in AOAC Official Method 990.21, Solid-Not-Fat in Milk By Difference between Total Solids and Fat Contents.

(3) Titratable acidity—As determined by the methods prescribed in AOAC Official Method 947.05, Acidity of Milk Titrimetric Method or by an equivalent potentiometric method.

* * * * *

■ 6. In § 131.112, revise paragraphs (d)(8) and (e) to read as follows:

§ 131.112 Cultured milk.

* * * * *

(d) * * *

(8) Salt or salt substitute.

* * * * *

(e) *Methods of analysis.* Referenced methods are from ''Official Methods of Analysis'' (incorporated by reference, see § 131.10):

(1) Milkfat content—As determined by the method prescribed in AOAC Official Method 989.05, Fat in Milk Modified Mojonnier Ether Extraction Method.

(2) Milk solids not fat content—Calculated by subtracting the milkfat content from the total solids content using the method prescribed in AOAC Official Method 990.21, Solid-Not-Fat in Milk By Difference between Total Solids and Fat Contents.

(3) Titratable acidity—As determined by the methods prescribed in AOAC Official Method 947.05, Acidity of Milk Titrimetric Method or by an equivalent potentiometric method.

* * * * *

■ 7. In § 131.160, revise paragraphs (b)(5) and (c) to read as follows:

§ 131.160 Sour cream.

* * * * *

(b) * * *

(5) Salt or salt substitute.

* * * * *

(c) *Methods of analysis.* Referenced methods are from ''Official Methods of Analysis'' (incorporated by reference, see § 131.10).

(1) Milkfat content—AOAC Official Method 945.48G, under Evaporated Milk (Unsweetened).

(2) Titratable acidity—AOAC Official Method 947.05, Acidity of Milk Titrimetric Method.

* * * * *

■ 8. In § 131.162, revise paragraphs (b)(4) and (c) to read as follows:

§ 131.162 Acidified sour cream.

* * * * *

(b) * * *

(4) Salt or salt substitute.

* * * * *

(c) *Methods of analysis.* Referenced methods are from ''Official Methods of Analysis'' (incorporated by reference, see § 131.10).

(1) Milkfat content—AOAC Official Method 945.48G, under Evaporated Milk (Unsweetened).

(2) Titratable acidity—AOAC Official Method 947.05, Acidity of Milk Titrimetric Method.

* * * * *

■ 9. In § 131.170, revise paragraphs (e)(2) and (f) to read as follows:

§ 131.170 Eggnog.

* * * * *

(e) * * *

(2) Salt or salt substitute.

* * * * *

(f) *Methods of analysis.* Referenced methods are from ''Official Methods of Analysis'' (incorporated by reference, see § 131.10).

(1) Milkfat content—As determined by the method prescribed in AOAC Official Method 989.05, Fat in Milk Modified Mojonnier Ether Extraction Method.

(2) Milk solids not fat content—Calculated by subtracting the milkfat content from the total solids content using the method prescribed in AOAC Official Method 990.21, Solid-Not-Fat in Milk By Difference between Total Solids and Fat Contents.

* * * * *

PART 133—CHEESES AND RELATED CHEESE PRODUCTS

■ 10. The authority citation for part 133 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 11. In § 133.102, add paragraph (c)(3) to read as follows:

§ 133.102 Asiago fresh and asiago soft cheese.

* * * * *

(c) * * *

(3) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 12. In § 133.106, add paragraph(b)(3)(vii) to read as follows:

§ 133.106 Blue cheese.

* * * * *

(b) * * *

(3) * * *

(vii) Salt substitute.

* * * * *

■ 13. In § 133.108, add paragraph (b)(3)(v) to read as follows:

§ 133.108 Brick cheese.

* * * * *

(b) * * *

(3) * * *

(v) Salt substitute.

* * * * *

■ 14. In § 133.111, add paragraph (c)(3) to read as follows:

§ 133.111 Caciocavallo siciliano cheese.

* * * * *

(c) * * *

(3) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 15. In § 133.113, add paragraph (b)(3)(vi) to read as follows:

§ 133.113 Cheddar cheese.

* * * * *

(b) * * *

(3) * * *

(vi) Salt substitute.

* * * * *

■ 16. In § 133.118, revise the first sentence of paragraph (c)(2) and add paragraph (c)(4) to read as follows:

§ 133.118 Colby cheese.

* * * * *

(c) * * *

(2) Milk shall be deemed to have been pasteurized if it has been held at a temperature of not less than 145 °F for a period of not less than 30 minutes, or for a time and at a temperature equivalent thereto in phosphatase destruction. * * *

* * * * *

(4) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 17. In § 133.123, revise paragraph (c)(3) to read as follows:

§ 133.123 Cold-pack and club cheese.

* * * * *

(c) * * *

(3) Salt or salt substitute.

* * * * *

■ 18. In § 133.124, revise paragraph (e)(3) to read as follows:

§ 133.124 Cold-pack cheese food.

* * * * *

(e) * * *

(3) Salt or salt substitute.

* * * * *

■ 19. In § 133.127, revise paragraph (b)(3)(v) to read as follows:

§ 133.127 Cook cheese, koch kaese.

* * * * *

(b) * * *

(3) * * *

(v) Salt or salt substitute.

* * * * *

■ 20. In § 133.129, revise paragraphs (b)(1)(i) through (b)(1)(iii) to read as follows:

§ 133.129 Dry curd cottage cheese.

* * * * *

(b) * * *

(1) * * *

(i) Harmless lactic-acid-producing bacteria, with or without rennet and/or other safe and suitable milk-clotting enzyme that produces equivalent curd formation, are added and it is held until it becomes coagulated. The coagulated mass may be cut; it may be warmed; it may be stirred; it is then drained. The curd may be washed with water and further drained; it may be pressed, chilled, worked, seasoned with salt or salt substitute; or

(ii) Food grade phosphoric acid, lactic acid, citric acid, or hydrochloric acid, with or without rennet and/or other safe and suitable milk-clotting enzyme that produces equivalent curd formation, is added in such amount as to reach a pH of between 4.5 and 4.7; coagulation to a firm curd is achieved while heating to a maximum of 120 °F without agitation during a continuous process. The coagulated mass may be cut; it may be warmed; it may be stirred; it is then drained. The curd is washed with water, stirred, and further drained. It may be pressed, chilled, worked, seasoned with salt or salt substitute.

(iii) Food grade acids as provided in paragraph (b)(1)(ii) of this section, D-Glucono-delta-lactone with or without rennet, and/or other safe and suitable milk clotting enzyme that produces equivalent curd formation, are added in such amounts as to reach a final pH value in the range of 4.5—4.8, and it is held until it becomes coagulated. The coagulated mass may be cut; it may be warmed; it may be stirred; it is then drained. The curd is then washed with water, and further drained. It may be pressed, chilled, worked, and seasoned with salt or salt substitute.

* * * * *

■ 21. In § 133.133, revise paragraph (b)(3)(i) to read as follows:

§ 133.133 Cream cheese.

* * * * *

(b) * * *

(3) * * *

(i) Salt or salt substitute.

* * * * *

■ 22. In § 133.136, add paragraph (b)(3)(vi) to read as follows:

§ 133.136 Washed curd and soaked curd cheese.

* * * * *

(b) * * *

(3) * * *

(vi) Salt substitute.

* * * * *

■ 23. In § 133.138, add paragraph (b)(3)(v) to read as follows:

§ 133.138 Edam cheese.

* * * * *

(b) * * *

(3) * * *

(v) Salt substitute.

* * * * *

■ 24. In § 133.141, add paragraph (b)(3)(vii) to read as follows:

§ 133.141 Gorgonzola cheese.

* * * * *

(b) * * *

(3) * * *

(vii) Salt substitute.

* * * * *

■ 25. In § 133.144, add paragraph (b)(3)(vi) to read as follows:

§ 133.144 Granular and stirred curd cheese.

* * * * *

(b) * * *

(3) * * *

(vi) Salt substitute.

* * * * *

■ 26. In § 133.147, revise paragraph (c)(5) to read as follows:

§ 133.147 Grated American cheese food.

* * * * *

(c) * * *

(5) Salt or salt substitute.

* * * * *

■ 27. In § 133.148, revise paragraph (c) to read as follows:

§ 133.148 Hard grating cheeses.

* * * * *

(c)(1) For the purposes of this section, the word ''milk'' means cow's milk or goat's milk or sheep's milk or mixtures of two or all of these. Such milk may be adjusted by separating part of the fat therefrom or (in the case of cow's milk) by adding one or more of the following: Cream, skim milk, concentrated skim milk, nonfat dry milk; (in the case of goat's milk) the corresponding products from goat's milk; (in the case of sheep's milk) the corresponding products from sheep's milk; water in a quantity sufficient to reconstitute any such concentrated or dried products used.

(2) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 28. In § 133.149, add paragraph (b)(3)(iv) to read as follows:

§ 133.149 Gruyere cheese.

* * * * *

(b) * * *

(3) * * *

(iv) Salt substitute.

* * * * *

■ 29. In § 133.150, revise the first sentence of paragraph (c)(2), add paragraph (c)(3), and revise paragraph (e)(1) to read as follows:

§ 133.150 Hard cheeses.

* * * * *

(c) * * *

(2) Milk shall be deemed to have been pasteurized if it has been held at a temperature of not less than 145 °F for a period of not less than 30 minutes, or for a time and at a temperature equivalent thereto in phosphatase destruction. * * *

(3) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

(e) * * *

(1) The specific common or usual name of such hard cheese, if any such name has become generally recognized therefor; or

* * * * *

■ 30. In § 133.152, add paragraph (b)(3)(iv) to read as follows:

§ 133.152 Limburger cheese.

* * * * *

(b) * * *

(3) * * *

(iv) Salt substitute.

* * * * *

■ 31. In § 133.153, revise paragraph (b)(3)(iii) to read as follows:

§ 133.153 Monterey cheese and Monterey jack cheese.

* * * * *

(b) * * *

(3) * * *

(iii) Salt or salt substitute.

* * * * *

■ 32. In § 133.155, revise paragraph (b)(3)(iii) to read as follows:

§ 133.155 Mozzarella cheese and scamorza cheese.

* * * * *

(b) * * *

(3) * * *

(iii) Salt or salt substitute.

* * * * *

■ 33. In § 133.156, revise paragraph (b)(3)(iii) to read as follows:

§ 133.156 Low-moisture mozzarella and scamorza cheese.

* * * * *

(b) * * *

(3) * * *

(iii) Salt or salt substitute.

* * * * *

■ 34. In § 133.160, add paragraph (b)(3)(vi) to read as follows:

§ 133.160 Muenster and munster cheese.

* * * * *

(b) * * *

(3) * * *

(vi) Salt substitute.

* * * * *

■ 35. In § 133.162, revise paragraph (b)(3)(i) to read as follows:

§ 133.162 Neufchatel cheese.

* * * * *

(b) * * *

(3) * * *

(i) Salt or salt substitute.

* * * * *

■ 36. In § 133.164, add paragraph (b)(3)(iv) to read as follows:

§ 133.164 Nuworld cheese.

* * * * *

(b) * * *

(3) * * *

(iv) Salt substitute.

* * * * *

■ 37. In § 133.165, add paragraph (c)(3) to read as follows:

§ 133.165 Parmesan and reggiano cheese.

* * * * *

(c) * * *

(3) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 38. In § 133.169, revise paragraph (d)(4) to read as follows:

§ 133.169 Pasteurized process cheese.

* * * * *

(d) * * *

(4) Salt or salt substitute.

* * * * *

■ 39. In § 133.173, revise paragraph (e)(4) to read as follows:

§ 133.173 Pasteurized process cheese food.

* * * * *

(e) * * *

(4) Salt or salt substitute.

* * * * *

■ 40. In § 133.179, revise paragraph (f)(5) to read as follows:

§ 133.179 Pasteurized process cheese spread.

* * * * *

(f) * * *

(5) Salt or salt substitute.

* * * * *

■ 41. In § 133.181, add paragraph (b)(3)(vi) to read as follows:

§ 133.181 Provolone cheese.

* * * * *

(b) * * *

(3) * * *

(vi) Salt substitute.

* * * * *

■ 42. In § 133.182, revise the tenth sentence in paragraph (b) and revise paragraph (c)(2) to read as follows:

§ 133.182 Soft ripened cheeses.

* * * * *

(b) * * * Salt or salt substitute may be added during the procedure. * * *

* * * * *

(c) * * *

(2) Milk shall be deemed to have been pasteurized if it has been held at a

temperature of not less than 145 °F for a period of not less than 30 minutes, or for a time and at a temperature equivalent thereto in phosphatase destruction.

* * * * *

■ 43. In § 133.183, add paragraph (c)(3) to read as follows:

§ 133.183 Romano cheese.

* * * * *

(c) * * *

(3) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 44. In § 133.184, revise paragraphs (b) introductory text and (b)(3) to read as follows:

§ 133.184 Roquefort cheese, sheep's milk blue-mold, and blue-mold cheese from sheep's milk.

* * * * *

(b) *Optional Ingredients.* The following safe and suitable ingredients may be used:

* * * * *

(3) *Other optional ingredients.*

(i) Enzymes of animal, plant, or microbial origin, used in curing or flavor development.

(ii) Salt substitute.

* * * * *

■ 45. In § 133.185, add paragraph (b)(3)(v) to read as follows:

§ 133.185 Samsoe cheese.

* * * * *

(b) * * *

(3) * * *

(v) Salt substitute.

* * * * *

■ 46. In § 133.186, revise paragraphs (a)(2) and (c) to read as follows:

§ 133.186 Sap sago cheese.

(a) * * *

(2) One or more of the dairy ingredients specified in paragraph (b)(1) of this section is allowed to become sour, and is heated to boiling temperature, with stirring. Sufficient sour whey is added to precipitate the casein. The curd is removed, spread out in boxes, and pressed, and while under pressure is allowed to drain and ferment. It is ripened for not less than 5 weeks. The ripened curd is dried and ground; salt or salt substitute and dried clover of the species *Melilotus coerulea* are added. The mixture is shaped into truncated cones and ripened. The optional ingredient in paragraph (b)(2) of this section may be added during this procedure.

* * * * *

(c) *Nomenclature.* The name of the food is ''sap sago cheese.''

* * * * *

■ 47. In § 133.187, revise the tenth sentence of paragraph (b) and the first sentence of paragraph (c)(2) to read as follows:

§ 133.187 Semisoft cheeses.

* * * * *

(b) * * * Salt or salt substitute may be added during the procedure. * * *

* * * * *

(c) * * *

(2) Milk shall be deemed to have been pasteurized if it has been held at a temperature of not less than 145 °F for a period of not less than 30 minutes, or for a time and at a temperature equivalent thereto in phosphatase destruction. * * *

* * * * *

■ 48. In § 133.188, revise the tenth sentence in paragraph (b) and the first sentence in paragraph (c)(2) to read as follows:

§ 133.188 Semisoft part-skim cheeses.

* * * * *

(b) * * * Salt or salt substitute may be added during the procedure. * * *

* * * * *

(c) * * *

(2) Milk shall be deemed to have been pasteurized if it has been held at a temperature of not less than 145 °F for a period of not less than 30 minutes, or for a time and at a temperature equivalent thereto in phosphatase destruction. * * *

* * * * *

■ 49. In § 133.189, revise paragraph (d) to read as follows:

§ 133.189 Skim milk cheese for manufacturing.

* * * * *

(d)(1) For the purposes of this section, ''skim milk'' means cow's milk from which the milk fat has been separated.

(2) During the cheesemaking process, where the curd is salted, salt substitute may be used.

* * * * *

■ 50. In § 133.190, revise paragraph (b)(3)(iii) to read as follows:

§ 133.190 Spiced cheeses.

* * * * *

(b) * * *

(3) * * *

(iii) Salt or salt substitute.

* * * * *

■ 51. In § 133.195, add paragraph (b)(3)(vii) to read as follows:

§ 133.195 Swiss and emmentaler cheese.

* * * * *

(b) * * *

(3) * * *

(vii) Salt substitute.

* * * * *

PART 136—BAKERY PRODUCTS

■ 52. The authority citation for part 136 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 53. In § 136.110, revise paragraphs (c)(4) and (d) to read as follows:

§ 136.110 Bread, rolls, and buns.

* * * * *

(c) * * *

(4) Salt or salt substitute.

* * * * *

(d) Total solids are determined by the method prescribed in AOAC Official Method 935.36(a), Solids (Total) in Bread, except that if the baked unit weighs 454 grams (1 pound) or more, one entire unit is used for the determination; if the baked unit weighs less than 454 grams, enough units to weigh 454 grams or more are used. AOAC Official Method 935.36(a), Solids (Total) in Bread, ''Official Methods of Analysis,'' 21st Ed. (2019), is incorporated by reference into this section with the approval of the Director of the Federal Register under 5 U.S.C 552(a) and 1 CFR part 51. This incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* This material is also available from AOAC INTERNATIONAL, 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

* * * * *

PART 137—CEREAL FLOURS AND RELATED PRODUCTS

■ 54. The authority citation for part 137 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 55. Add subpart A, consisting of §§ 137.1 through 137.100, to read as follows:

Subpart A—General Provisions.

Sec.

137.10 Incorporation by reference.

137.20 through 137.100 [Reserved]

Subpart A—General Provisions.

§ 137.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622:

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) AOAC Official Method 923.02A, Reagent; IBR §§ 137.180(c); 137.270(b).

(2) AOAC Official Method 923.02B, Apparatus, under Carbon Dioxide (Total) in Baking Powders Gasometric Determination; IBR §§ 137.180(c); 137.270(b).

(3) Reference Table 909.04, Correction Factors for Gasometric Determination of Carbon Dioxide; IBR §§ 137.180(c); 137.270(b).

(b) [Reserved]

§§ 137.20 through 137.100 [Reserved]

■ 56. In § 137.180, revise paragraphs (a), (c) introductory text, and (c)(1) to read as follows:

§ 137.180 Self-rising flour.

(a) *Description.* Self-rising flour, self-rising white flour, self-rising wheat flour, is an intimate mixture of flour, sodium bicarbonate, and one or more of the acid-reacting substances monocalcium phosphate, sodium acid pyrophosphate, and sodium aluminum phosphate. It is seasoned with salt or salt substitute. When it is tested by the method prescribed in paragraph (c) of this section, not less than 0.5 percent of carbon dioxide is evolved. The acid-reacting substance is added in sufficient quantity to neutralize the sodium bicarbonate. The combined weight of such acid-reacting substance and sodium bicarbonate is not more than 4.5 parts to each 100 parts of flour used. Subject to the conditions and restrictions prescribed by § 137.105(a), the bleaching ingredients specified in such section may be added as optional ingredients. If the flour used in making the self-rising flour is bleached, the optional bleaching ingredient used therein (see § 137.105(a)) is also an optional ingredient of the self-rising flour.

* * * * *

(c) *Method of analysis.* Follow the method prescribed in AOAC Official Method 923.02A, Reagent, and 923.02B, Apparatus, under Carbon Dioxide (Total) in Baking Powders Gasometric Determination (incorporated by reference, see § 137.10): Instead of using AOAC Official Method 923.02C, Determination, use the following procedure:

(1) Weigh 17 grams of the official sample into flask A, add 15–20 glass beads (4–6 mm. diameter), and connect this flask with the apparatus (fig. 923.02). Open stopcock C and by means of the leveling bulb E bring the displacement solution to the 25 cc. graduation above the zero mark. (This 25 cc. is a partial allowance for the volume of acid to be used in the decomposition.) Allow the apparatus to stand 1–2 minutes to ensure that the temperature and pressure within the apparatus are the same as those of the room. Close the stopcock, lower the leveling bulb somewhat to reduce the pressure within the apparatus, and slowly run into the decomposition flask from burette F 45 cc. of sulfuric acid (1 + 5). To prevent the liberated carbon dioxide from escaping through the acid burette into the air, keep the displacement solution in the leveling bulb at all times during the decomposition at a lower level than that in the gas-measuring tube. Rotate and then vigorously agitate the decomposition flask for 3 minutes to mix the contents intimately. Allow to stand for 10 minutes to bring to equilibrium. Equalize the pressure in the measuring tube by means of the leveling bulb and read the volume of gas from the zero point on the tube. Deduct 20 cc. from this reading (this 20 cc. together with previous allowance of 25 cc. compensates for the 45 cc. acid used in the decomposition). Observe the temperature of the air surrounding the apparatus and also the barometric pressure and multiply the number of milliliters of gas evolved by the factor given in Reference Table 909.04, ''Correction Factors for Gasometric Determination of Carbon Dioxide'', incorporated by reference, see § 137.10) for the temperature and pressure observed. Divide the corrected reading by 100 to obtain the apparent percent by weight of carbon dioxide in the official sample.

* * * * *

■ 57. In § 137.270, revise paragraphs (a), (b) introductory text, and (b)(1) to read as follows:

§ 137.270 Self-rising white corn meal.

(a) *Description.* Self-rising white corn meal is an intimate mixture of white corn meal, sodium bicarbonate, and one or both of the acid-reacting substances monocalcium phosphate and sodium aluminum phosphate. It is seasoned with salt or salt substitute. When it is tested by the method prescribed in paragraph (b) of this section, not less than 0.5 percent of carbon dioxide is evolved. The acid-reacting substance is added in sufficient quantity to neutralize the sodium bicarbonate. The combined weight of such acid-reacting substance and sodium bicarbonate is not more than 4.5 parts to each 100 parts of white corn meal used.

(b) *Method of analysis.* Follow the method prescribed in AOAC Official Method 923.02A, Reagent, and 923.02B, Apparatus, under Carbon Dioxide (Total) in Baking Powders Gasometric Determination (incorporated by reference, see § 137.10): Instead of using AOAC Official Method 923.02C, Determination, use the following procedure:

(1) Weigh 17 grams of the official sample into flask A, add 15–20 glass beads (4–6 mm. diameter), and connect this flask with the apparatus (fig. 923.02). Open stopcock C and by means of the leveling bulk E bring the displacement solution to the 25 cc. graduation above the zero mark. (This 25 cc. is a partial allowance for the volume of acid to be used in the decomposition.) Allow the apparatus to stand 1–2 minutes to ensure that the temperature and pressure within the apparatus are the same as those of the room. Close the stopcock, lower the leveling bulb somewhat to reduce the pressure within the apparatus, and slowly run into the decomposition flask from burette F 45 cc. of sulfuric acid (1 + 5). To prevent the liberated carbon dioxide from escaping through the acid burette into the air, keep the displacement solution in the leveling bulb at all times during the decomposition at a lower level than that in the gas-measuring tube. Rotate and then vigorously agitate the decomposition flask for 3 minutes to mix the contents intimately. Allow to stand for 10 minutes to bring to equilibrium. Equalize the pressure in the measuring tube by means of the leveling bulb and read the volume of gas from the zero point on the tube. Deduct 20 cc. from this reading (this 20 cc. together with previous allowance of 25 cc. compensates for the 45 cc. acid used

in the decomposition). Observe the temperature of the air surrounding the apparatus and also the barometric pressure and multiply the number of milliliters of gas evolved by the factor given in the Reference Table 909.04, ''Correction Factors for Gasometric Determination of Carbon Dioxide'' (incorporated by reference, see § 137.10) for the temperature and pressure observed. Divide the corrected reading by 100 to obtain the apparent percent by weight of carbon dioxide in the official sample.

* * * * *

PART 139—MACARONI AND NOODLE PRODUCTS

■ 58. The authority citation for part 139 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 59. Add subpart A, consisting of §§ 1397.10 through 139.100, to read as follows:

Subpart A—General Provisions.

Sec.
139.10 Incorporation by reference.
139.20 through 139.100 [Reserved]

Subpart A—General Provisions.

§ 139.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) AOAC Official Method 926.07A, Vacuum Oven Method, under Solids (Total) and Loss on Drying (Moisture) in Macaroni Products; IBR §§ 139.110(a); 139.150(a).

(2) [Reserved]

(b) [Reserved]

§§ 139.20 through 139.100 [Reserved]

■ 60. In § 139.110, revise paragraphs (a)(4) and (5) to read as follows:

§ 139.110 Macaroni products.

(a) * * *

(4) Salt or salt substitute, in a quantity that seasons the food.

(5) Gum gluten, in such quantity that the protein content of the finished food is not more than 13 percent by weight. The finished macaroni product contains not less than 87 percent of total solids as determined by AOAC Official Method 926.07A(incorporated by reference, see § 139.10).

* * * * *

■ 61. In § 139.150, revise paragraphs (a)(2) and (4) to read as follows:

§ 139.150 Noodle products.

(a) * * *

(2) Salt or salt substitute, in a quantity that seasons the food.

* * * * *

(4) Concentrated glyceryl monostearate (containing not less than 90 percent monoester) in a quantity not exceeding 3 percent by weight of the finished food. The finished noodle product contains not less than 87 percent of total solids as determined by AOAC Official Method 926.07A(incorporated by reference, see § 139.10). The total solids of noodle products contains not less than 5.5 percent by weight of the solids of egg, or egg yolk.

* * * * *

PART 145—CANNED FRUITS

■ 62. The authority citation for part 145 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 63. In § 145.110, revise paragraphs (a)(1) and (a)(2)(iii) to read as follows:

§ 145.110 Canned applesauce.

(a) * * *

(1) *Definition.* Canned applesauce is the food prepared from comminuted or chopped apples (*Malus domestica* Borkhausen), which may or may not be peeled and cored, and which may have added thereto one or more of the optional ingredients specified in paragraph (a)(2) of this section. The apple ingredient is heated and, in accordance with good manufacturing practices, bruised apple particles, peel, seed, core material, carpel tissue, and other coarse, hard, or extraneous materials are removed. The food is sealed in containers. It is so processed by heat, either before or after sealing, as to prevent spoilage. The soluble solids content, measured by refractometer and expressed as percent sucrose (degrees Brix) with correction for temperature to the equivalent at 20 °C (68 °F), is not less than 9 percent (exclusive of the solids of any added optional nutritive carbohydrate sweeteners) as determined by AOAC Official Method 932.12 but without correction for invert sugar or other substances. AOAC Official Method 932.12, ''Solids (Soluble) in Fruits and Fruit Products,'' in ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 21st Ed. (2019), is incorporated by reference into this section with the approval of the Director of the Federal Register under 5 U.S.C. 552(a) and 1 CFR part 51,. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and the National Archives and Records Administration (NARA). Contact the FDA at FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* This material is available from AOAC INTERNATIONAL, 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

(2) * * *

(iii) Salt or salt substitute.

* * * * *

■ 64. In § 145.130, revise paragraph (a)(5) to read as follows:

§ 145.130 Canned figs.

(a) * * *

(5) Salt or salt substitute.

* * * * *

PART 150—FRUIT BUTTERS, JELLIES, PRESERVES, AND RELATED PRODUCTS

■ 65. The authority citation for part 150 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 66. Add subpart A, consisting of §§ 150.10 through 150.100, to read as follows:

Subpart A—General Provisions.

Sec.
150.10 Incorporation by reference.
150.20 through 150.100 [Reserved]

Subpart A—General Provisions.

§ 150.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration

(FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) AOAC Official Method 932.12, Solids (Soluble) in Fruits and Fruit Products; IBR § 150.110(d).

(2) AOAC Official Method 932.14C, By Means of Refractometer, under Solids in Syrups; IBR § 150.110(d).

(b) [Reserved]

§§ 150.20 through 150.100 [Reserved]

■ 67. In § 150.110, revise paragraphs (c)(4), (d)(3), and (d)(5) to read as follows:

§ 150.110 Fruit butter.

* * * * *

(c) * * *

(4) Salt or salt substitute.

* * * * *

(d) * * *

(3) The soluble solids content of the finished fruit butter is not less than 43 percent, as determined by AOAC Official Method 932.12 (incorporated by reference, see § 150.10).

* * * * *

(5) The weight of fruit juice or diluted fruit juice or concentrated fruit juice (optional ingredient, paragraph (c)(6) of this section) from a fruit specified in paragraph (b)(1) of this section is the weight of such juice, as determined by the method prescribed in paragraph (d)(2) of this section, except that the percent of soluble solids is determined by AOAC Official Method 932.14C, under Solids in Syrups (incorporated by reference, see § 150.10); the weight of diluted concentrated juice from any other fruits is the original weight of the juice before it was diluted or concentrated.

* * * * *

PART 155—CANNED VEGETABLES

■ 68. The authority citation for part 155 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379(e).

■ 69. Add § 155.10 to subpart A to read as follows:

§ 155.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definition of Terms and Explanatory Notes''; IBR §§ 155.120(b); 155.130(b).

(2) AOAC Official Method 938.10, Solids (Alcohol-Insoluble) in Canned Peas Gravimetric Method; IBR § 155.170(b).

(b) [Reserved]

■ 70. In § 155.120, revise paragraphs (a)(3)(i) and (b)(2)(i) to read as follows:

§ 155.120 Canned green beans and canned wax beans.

(a) * * *

(3) * * *

(i) Salt or salt substitute.

* * * * *

(b) * * *

(2) * * *

(i) Determine the gross weight of the container. Open and distribute the contents of the container over the meshes of a U.S. No. 8 circular sieve with openings of 2.36 mm (0.0937 in), which has been previously weighed. The diameter of the sieve is 20.3 cm (8 in) if the quantity of contents of the container is less than 1.36 kg (3 lbs) and 30.5 cm (12 in) if such quantity is 1.36 kg (3 lbs) or more. The bottom of the sieve is woven-wire cloth that complies with the specifications of such cloth set forth in ''Official Methods of Analysis'', Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definition of Terms and Explanatory Notes,'' (incorporated by reference, see § 155.10). Without shifting the material on the sieve, incline the sieve 17° to 20° to facilitate drainage. Two minutes after drainage begins, weigh the sieve and the drained material. Record in grams (ounces) the weight so found, less the weight of the sieve, as the drained weight. Dry and weigh the empty container and subtract this weight from the gross weight to obtain the net weight. Calculate the percent of drained liquid in the net weight.

* * * * *

■ 71. In § 155.130, revise paragraphs (a)(3)(i) and (b)(2)(i) to read as follows:

§ 155.130 Canned corn.

(a) * * *

(3) * * *

(i) Salt or salt substitute.

* * * * *

(b) * * *

(2) * * *

(i) Determine the gross weight of the container. Open and distribute the contents of the container over the meshes of a U.S. No. 8 circular sieve, which has previously been weighed. The diameter of the sieve is 20.3 cm. (8 in) if the quantity of the contents of the container is less than 1.36 kg. (3 lbs), and 30.5 cm. (12 in) if such quantity is 1.36 kg. (3 lbs) or more. The bottom of the sieve is woven-wire cloth that complies with the specifications for such sieve set forth in ''Official Methods of Analysis'', Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definition of Terms and Explanatory Notes'' (incorporated by reference, see § 155.10). Without shifting the material on the sieve, so incline the sieve at approximately 17° to 20° angle to facilitate drainage. Two minutes from the time drainage begins, weigh the sieve and the drained material. Record, in grams (ounces), the weight so found, less the weight of the sieve, as the drained weight. Dry and weigh the empty container and subtract this weight from the gross weight to obtain the net weight. Calculate the percent of drained liquid in the net weight.

* * * * *

■ 72. In § 155.170, revise paragraph (a)(2)(i), and paragraphs (b)(1)(iii) and (vi) to read as follows:

§ 155.170 Canned peas.

(a) * * *

(2) * * *

(i) Salt or salt substitute.

* * * * *

(b) * * *

(1) * * *

* * * * *

(iii) *Seriously blemished peas.* Not more than 1 percent of the drained weight is seriously blemished peas, *i.e.,* peas that are hard, shriveled, spotted,

discolored, or otherwise blemished to an extent that the appearance or eating quality is seriously affected.

* * * * *

(vi) *Alcohol-insoluble solids.* The alcohol-insoluble solids of smooth-skin or substantially smooth-skin peas, such as Alaska-type peas or hybrids having similar characteristics, may not be more than 23.5 percent and, of sweet green wrinkled varieties or hybrids having similar characteristics, not more than 21 percent based on the procedure set forth in tAOAC Official Method 938.10(incorporated by reference, see § 155.10).

* * * * *

■ 73. In § 155.190, revise paragraph (a)(2)(iv) to read as follows:

§ 155.190 Canned tomatoes.

(a) * * *

(2) * * *

(iv) Salt or salt substitute.

* * * * *

■ 74. In § 155.191, revise paragraph (a)(2)(i) to read as follows:

§ 155.191 Tomato concentrates.

(a) * * *

(2) * * *

(i) Salt or salt substitute (sodium chloride formed during acid neutralization shall be considered added salt).

* * * * *

■ 75. In § 155.194, revise paragraph (a)(1)(iv) to read as follows:

§ 155.194 Catsup.

(a) * * *

(1) * * *

(iv) The liquid obtained from the residue from partial extraction of juice from such tomatoes. Such liquid is strained so as to exclude skins, seeds, and other coarse or hard substances in accordance with current good manufacturing practice. Prior to straining, food-grade hydrochloric acid may be added to the tomato material in an amount to obtain a pH no lower than 2.0. Such acid is then neutralized with food-grade sodium hydroxide so that the treated tomato material is restored to a pH of 4.2 ± 0.2. The final composition of the food may be adjusted by concentration and/or by the addition of water. The food may contain salt or salt substitute (sodium chloride formed during acid neutralization shall be considered added salt) and is seasoned with ingredients as specified in paragraph (a)(2) of this section. The food is preserved by heat sterilization (canning), refrigeration, or freezing. When sealed in a container to be held at ambient temperatures, it is so processed by heat, before or after sealing, as to prevent spoilage.

* * * * *

■ 76. In § 155.200, revise paragraph (c)(4)(i) to read as follows:

§ 155.200 Certain other canned vegetables.

* * * * *

(c) * * *

(4) * * *

(i) Salt or salt substitute.

* * * * *

■ 77. In § 155.201, revise paragraph (a)(3)(i) to read as follows:

§ 155.201 Canned mushrooms.

(a) * * *

(3) * * *

(i) Salt or salt substitute.

* * * * *

PART 156—VEGETABLE JUICES

■ 78. The authority citation for part 156 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371.

■ 79. In § 156.145, revise paragraph (a)(1) to read as follows:

§ 156.145 Tomato juice.

(a) * * *

(1) *Definition.* Tomato juice is the food intended for direct consumption, obtained from the unfermented liquid extracted from mature tomatoes of the red or reddish varieties of *Lycopersicum esculentum* P. Mill, with or without scalding followed by draining. In the extraction of such liquid, heat may be applied by any method which does not add water thereto. Such juice is strained free from peel, seeds, and other coarse or hard substances, but contains finely divided insoluble solids from the flesh of the tomato in accordance with current good manufacturing practice. Such juice may be homogenized, may be seasoned with salt or salt substitute, and may be acidified with any safe and suitable organic acid. The juice may have been concentrated and later reconstituted with water and/or tomato juice to a tomato soluble solids content of not less than 5.0 percent by weight as determined by the method prescribed in § 156.3(b). The food is preserved by heat sterilization (canning), refrigeration, or freezing. When sealed in a container to be held at ambient temperatures, it is so processed by heat, before or after sealing, as to prevent spoilage.

* * * * *

PART 158—FROZEN VEGETABLES

■ 80. The authority citation for part 158 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371.

■ 81. In § 158.170, revise paragraphs (a)(1)(iv) and (b)(1)(iii) to read as follows:

§ 158.170 Frozen peas.

(a) * * *

(1) * * *

(iv) Salt or salt substitute.

* * * * *

(b) * * *

(1) * * *

(iii) Not more than 2 percent by weight seriously blemished peas, *i.e.,* peas that are hard, shriveled, spotted, discolored or otherwise blemished to an extent that the appearance or eating quality is seriously affected.

* * * * *

PART 161—FISH AND SHELLFISH

■ 82. The authority citation for part 161 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 83. Add § 161.10 to read as follows:

§ 161.10 Incorporation by reference.

Certain material is incorporated by reference into this part with the approval of the Director of the Federal Register in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and at the National Archives and Records Administration (NARA). Contact FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visitn *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* The material may be obtained from AOAC INTERNATIONAL (AOAC), 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622.

(a) Official Methods of Analysis, 21st Ed. (2019);

(1) Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definition of Terms and Explanatory Notes''; IBR §§ 161.145(c); 161.173(c); 161.190(a)(7).

(2) [Reserved]

(b) [Reserved]

■ 84. In § 161.145, revise paragraphs (a)(1) and (c)(3) to read as follows:

§ 161.145 Canned oysters.

(a) * * *

(1) Canned oysters is the food prepared from one or any mixture of two or all of the forms of oysters

specified in paragraph (a)(2) of this section, and a packing medium of water, or the watery liquid draining from oysters before or during processing, or a mixture of such liquid and water. The food may be seasoned with salt or salt substitute. It is sealed in containers and so processed by heat as to prevent spoilage.

* * * * *

(c) * * *

(3) Drained weight is determined by the following method: Keep the unopened canned oyster container at a temperature of not less than 68 °F or more than 95 °F for at least 12 hours immediately preceding the determination. After opening, tilt the container so as to distribute its contents evenly over the meshes of a circular sieve that has been previously weighed. The diameter of the sieve is 8 inches if the quantity of the contents of the container is less than 3 pounds and 12 inches if such quantity is 3 pounds or more. The bottom of the sieve is woven-wire cloth that complies with the specifications for such cloth set forth under ''2.36 mm (No. 8)'' in ''Official Methods of Analysis,'' Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definition of Terms and Explanatory Notes,'' (incorporated by reference, see § 161.10). Without shifting the material on the sieve, so incline the sieve as to facilitate drainage. Two minutes from the time drainage begins, weigh the sieve and the drained oysters. The weight so found, less the weight of the sieve, shall be considered to be the drained weight of the oysters.

* * * * *

■ 85. In § 161.170, revise paragraph (a)(4)(i) to read as follows:

§ 161.170 Canned Pacific salmon.

(a) * * *

(4) * * *

(i) Salt or salt substitute.

* * * * *

■ 86. In § 161.173, revise paragraphs (a)(4)(i) and (c)(1) to read as follows:

§ 161.173 Canned wet pack shrimp in transparent or nontransparent containers.

(a) * * *

(4) * * *

(i) Salt or salt substitute.

* * * * *

(c) * * *

(1) The standard of fill of transparent or nontransparent containers for canned wet pack shrimp is a fill such that the cut-out weight of shrimp taken from each container is not less than 60 percent of the weight of the water required to fill the container. The weight of the water required to fill the container is determined by the general method provided in § 130.12(a) of this chapter. Cut-out weight is determined by the following method: Keep the unopened canned shrimp container at a temperature of not less than 68 °F nor more than 75 °F for at least 12 hours immediately preceding the determination. After opening, distribute the shrimp evenly over the meshes of a circular sieve that has been previously weighed. The diameter of the sieve is 20.3 centimeters (8 inches) if the quantity of the contents of the container is less than 1.36 kilograms (3 pounds), and 30.5 centimeters (12 inches) if such quantity is 1.36 kilograms (3 pounds) or more. The bottom of the sieve is woven-wire cloth that complies with the specifications for such cloth set forth as a 2.36 mm (No. 8) sieve in ''Official Methods of Analysis'' (incorporated by reference, see § 161.10), Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series), under the heading ''Definition of Terms and Explanatory Notes'' (incorporated by reference, see § 161.10) Without shifting the material on the sieve, incline the sieve at an angle of approximately 17° to 20° to facilitate drainage. Allow the shrimp to drain for 2 minutes, measured from the moment the product is poured onto the sieve. Weigh the sieve and the drained shrimp. The weight so found, less the weight of the sieve, shall be considered to be the cut-out weight of the shrimp.

* * * * *

■ 87. In § 161.190, revise paragraphs (a)(6)(i) and (a)(7) introductory text to read as follows:

§ 161.190 Canned tuna.

(a) * * *

(6) * * *

(i) Salt or salt substitute.

* * * * *

(7) For determination of the color designations specified in paragraph (a)(4) of this section, the following method shall be used: Recombine the separations of pressed cake resulting from the method prescribed in paragraph (c)(2) of this section. Pass the combined portions through a sieve fitted with woven-wire cloth of ¼-inch mesh complying with the specifications for such cloth set forth in ''Official Methods of Analysis'', Table 1, ''Nominal Dimensions of Standard Test Sieves (USA Standard Series),'' under the heading ''Definitions of Terms and Explanatory Notes'' (incorporated by reference, see § 161.10) Mix the sieved material and place a sufficient quantity into a 307 × 113 size container (bearing a top seam and having a false bottom approximately ½-inch deep and painted flat black inside and outside) so that after tamping and smoothing the surface of the sample the material will be ⅛-inch to ¼-inch below the top of the container. Within 10 minutes after sieving through the ¼-inch mesh woven-wire cloth, determine the Munsell value of sample surface.

* * * * *

PART 163—CACAO PRODUCTS

■ 88. The authority citation for part 163 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 341, 343, 348, 371, 379e.

■ 89. In § 163.111, revise paragraph (b)(6) to read as follows:

§ 163.111 Chocolate liquor.

* * * * *

(b) * * *

(6) Salt or salt substitute.

* * * * *

■ 90. In § 163.112, revise paragraph (b)(4) to read as follows:

§ 163.112 Breakfast cocoa.

* * * * *

(b) * * *

(4) Salt or salt substitute.

* * * * *

■ 91. In § 163.123, revise paragraph (b)(3) to read as follows:

§ 163.123 Sweet chocolate.

* * * * *

(b) * * *

(3) Spices, natural and artificial flavorings, ground whole nut meats, ground coffee, dried malted cereal extract, salt or salt substitute, and other seasonings that do not either singly or in combination impart a flavor that imitates the flavor of chocolate, milk, or butter;

* * * * *

■ 92. In § 163.124, revise paragraph (b)(4) to read as follows:

§ 163.124 White chocolate.

* * * * *

(b) * * *

(4) Spices, natural and artificial flavorings, ground whole nut meats, ground coffee, dried malted cereal extract, salt or salt substitute, and other seasonings that do not either singly or in combination impart a flavor that imitates the flavor of chocolate, milk, or butter;

* * * * *

■ 93. In § 163.130, revise paragraph (b)(3) to read as follows:

§ 163.130 Milk chocolate.

* * * * *

(b) * * *

(3) Spices, natural and artificial flavorings, ground whole nut meats, ground coffee, dried malted cereal extract, salt or salt substitute, and other seasonings that do not either singly or in combination impart a flavor that imitates the flavor of chocolate, milk, or butter;

PART 166—MARGARINE

■ 94. The authority citation for part 166 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 347, 348, 371, 379e.

■ 95. In § 166.110, revise paragraphs (a) and (b)(2) to read as follows:

§ 166.110 Margarine.

(a) *Description.* Margarine (or oleomargarine) is the food in plastic form or liquid emulsion, containing not less than 80 percent fat determined by the method prescribed in AOAC Official Method 938.06A. AOAC Official Method 938.06A, ''Indirect Method, under Fat in Butter,'' found in ''Official Methods of Analysis of AOAC INTERNATIONAL,'' 21st Ed. (2019), is incorporated by reference into this section with the approval of the Director of the Federal Register under 5 U.S.C. 552(a) and 1 CFR part 51. All approved incorporation by reference (IBR) material is available for inspection at the Food and Drug Administration (FDA) and the National Archives and Records Administration (NARA). Contact the FDA at FDA's Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500. For information on the availability of this material at NARA, visit *www.archives.gov/federal-register/cfr/ibr-locations* or email *fr.inspection@nara.gov.* This material is available from AOAC INTERNATIONAL, 2275 Research Blvd., Suite 300, Rockville, MD 20850–3250, 1–800–379–2622. Margarine contains only safe and suitable ingredients, as defined in § 130.3(d) of this chapter. It is produced from one or more of the optional ingredients in paragraph (a)(1) of this section, and one or more of the optional ingredients in paragraph (a)(2) of this section, to which may be added one or more of the optional ingredients in paragraph (b) of this section. Margarine contains vitamin A as provided for in paragraph (a)(3) of this section.

* * * * *

(b) * * *

(2) Salt (sodium chloride) or salt substitute; potassium chloride for dietary margarine or oleomargarine.

* * * * *

PART 168—SWEETENERS AND TABLE SIRUPS

■ 96. The authority citation for part 168 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 97. In § 168.130, revise paragraph (b)(1) to read as follows:

§ 168.130 Cane sirup.

* * * * *

(b) * * *

(1) Salt or salt substitute.

* * * * *

■ 98. In § 168.140, revise the first sentence of paragraph (a) and paragraph (b)(1) to read as follows:

§ 168.140 Maple sirup.

(a) Maple sirup is the liquid food derived by concentration and heat treatment of the sap of the maple tree (Acer) or by solution in water of maple sugar (maple concrete) made from such sap. * * *

(b) * * *

(1) Salt or salt substitute.

* * * * *

■ 99. In § 168.160, revise paragraph (b)(1) to read as follows:

§ 168.160 Sorghum sirup.

* * * * *

(b) * * *

(1) Salt or salt substitute.

* * * * *

■ 100. In § 168.180, revise paragraph (b)(7) to read as follows:

§ 168.180 Table sirup.

* * * * *

(b) * * *

(7) Salt or salt substitute.

* * * * *

PART 169—FOOD DRESSINGS AND FLAVORINGS

■ 101. The authority citation for part 169 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 343, 348, 371, 379e.

■ 102. In § 169.140, revise paragraph (d)(1) to read as follows:

§ 169.140 Mayonnaise.

* * * * *

(d) * * *

(1) Salt or salt substitute.

* * * * *

■ 103. In § 169.150, revise paragraph (e)(1) to read as follows:

§ 169.150 Salad dressing.

* * * * *

(e) * * *

(1) Salt or salt substitute.

* * * * *

Dated: March 23, 2023.

Robert M. Califf,

Commissioner of Food and Drugs.

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Comprehensive REVIEWS in Food Science and Food Safety

Dietary Food-Additive Phosphate and Human Health Outcomes

Allison Cooke

Abstract: Dietary intake of phosphorus is required for human health, and dietary reference intakes for phosphorus have been established. Food-grade phosphates are used as additives to provide a wide range of technical functions in food production. Phosphates are often the most efficient ingredients to provide the required functionality in many applications, and in some cases, there are not effective and approved alternatives. However, many investigators have expressed concern about the quantities of phosphorus and food-additive phosphate present in the diets of many populations. This paper presents the outcome of an extensive review of 110 primary research articles focused on identifying evidence that substantiates or refutes associations of total dietary phosphorus and food-additive phosphate intake with health and disease in humans. The lack of conclusive evidence prevented the drawing of firm conclusions about the safety and possible risks of food-additive phosphate in the general population, which is consonant with the overall assessments of authoritative institutions who have concluded that available data are insufficient to make the required determinations. Despite the inadequacy of the evidence currently available, many of the authors of the publications reviewed for this paper expressed concerns about the quantities of phosphorus and food-additive phosphate in the diets of the populations and subpopulations they studied. At the same time, most of these authors offered only qualified conclusions and expressed themselves tentatively. In addition, authors of primary research publications, authors of review articles, and authoritative institutions have called for the conduct of further research.

Keywords: dietary phosphate, dietary phosphorus phosphate, phosphate additive, serum phosphorus

Executive Summary

Phosphorus is integral to many central metabolic processes and is an essential constituent of anatomical structure. Dietary intake of phosphorus (in the form of organic and inorganic phosphates) is required for human health, and dietary reference intakes for phosphorus have been published that include estimates of average requirements and recommended dietary allowances. Not all authoritative bodies have provided tolerable upper intake levels for dietary phosphorus, however, and many investigators have expressed concern about the quantities of phosphorus and food-additive phosphate present in the diets of many populations, quantities they believe to be excessive and possibly injurious to health.

Food-grade phosphates are used as additives in food production to function as buffers, sequestrants, acidulants, bases, flavors, cryoprotectants, gel accelerants, dispersants, nutrients, or precipitants, as well as to function as free-flow or ion-exchange agents. Food-grade phosphates are used to chemically leaven cakes, cookies, pancakes, waffles, and donuts; to maintain the structure and hydration of meat, poultry, and seafood products; to improve fluidity of evaporated milk; flavor or add minerals to beverages; and to maintain the structure of canned fruit and vegetable products. Phosphates are often the most efficient ingredients to provide the required functionality in these applications, and in some cases, there are not effective and approved alternatives. Some food-additive phosphates contain minerals other than phosphate (such as calcium, potassium, and magnesium) that are consumed by some populations in quantities below those recommended in guidelines.

This white paper presents the outcome of an extensive literature review focused on identifying evidence that substantiates or refutes associations of total dietary phosphorus and food-additive phosphate intake with health and disease in humans. Relevant primary research articles published from 1995 to January 2016 were reviewed. Only 2 primary research publications were identified that focused on data potentially specific to a direct association between a phosphorus food additive and a clinical outcome; both reported observational studies. The majority of the publications presented only indirect evidence. These publications reported findings regarding associations, noncausal or causal, between dietary food-additive phosphate intake; total dietary intake of phosphorus; phosphorus absorption and excretion; serum phosphorus concentration; relevant hormonal and other physiological changes; relevant target organ function and biomarkers of such function; and health or morbidity and mortality. The paucity of direct evidence, the limited amount of indirect evidence, and the inability of data from observational studies to support causal relationships are discussed in several of the publications reviewed for the white paper.

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The review included a total of 110 primary research articles. Only 11 (10%) of these articles focused on various associations of dietary food-additive phosphates or phosphoric acid; 2 of these articles (2%) examined the associations of dietary food-additive phosphorus (specifically, phosphoric acid) with morbidity (and none with mortality). Half of the articles (55 [50%]) focused on various associations of total phosphorus content in the diet. Of all the articles reviewed, 38 (35%) had morbidity or mortality as endpoints. Only 36 (33%) of the studies reviewed were interventional, thereby allowing determination of causal relationships.

Of the studies included in the white paper that examined various associations of dietary food-additive phosphorus, very few specified which compounds were under investigation as additives. The (usually implicit) assumption in the studies was that changes in total dietary phosphorus intake or absorption resulting from the inclusion of food-additive phosphorus in the diet were central to the investigation and not the specific phosphorus additive(s) ingested.

Analysis of the studies revealed an array of methodological limitations. Some of these limitations were common to many of the studies; every study was affected by at least one of the limitations. The limitations weakened the reliability of the findings of the studies, decreased the strength of the evidence they could provide for or against the safety of dietary food-additive phosphate, and accounted, in part, for the numerous inconsistencies among the studies in their findings. These methodological limitations included the following:

- Noninterventional study design, precluding assessment of possible causal roles of factors investigated
- Probable bias of findings by unrecognized confounding factors, notably in studies examining morbidity or mortality; incorporation of different selections of recognized confounders into the various statistical models employed within and across studies
- Inherent difficulties in determining dietary phosphorus intake and, in particular, the intake of food-additive phosphate: the inherent limitations of widely used dietary ascertainment methods, such as 24-h dietary recall and food frequency questionnaires; likely inaccuracies in nutrient composition tables
- Inherent difficulties in determining the quantity of phosphorus absorbed from the diet
- The complex interrelationships between dietary phosphorus, conutrients (notably, calcium), and different foods, and the consequent difficulties of isolating the effects or noncausal associations of dietary phosphorus itself; difficulties in assessing the proportional contribution of food-additive phosphate to total dietary phosphorus intake and the effects of food-additive phosphate on total dietary intake
- The latencies, likely to be long, between dietary exposure and its effects on morbidity or mortality; the unproven validity of potential surrogate markers of morbidity and mortality, notably serum phosphorus concentration, that were assessed in studies of shorter duration; and widely varying durations of subject participation across the studies reviewed
- Differing boundaries used to define categories of dietary phosphorus intake across studies, and the variable relationships of these boundaries to dietary recommendations and *de facto* population intakes
- The diverse nature of the populations studied and their characteristic diets, the location of these populations in different countries, and changing dietary habits and methods of food production over the 20-y period during which the publications reviewed for the white paper were published.

These and other limitations were discussed in many of the primary research publications reporting affected studies.

The number of relevant studies in each area that was identified for separate analysis in the white paper was small, and even when analyses were confined to the few studies within a given area, data were often discordant or difficult to compare across studies. For example, higher dietary phosphorus intake was associated with an increase in cancer risk in 2 of 6 studies examining prostate cancer incidence: the other 4 prostate cancer studies found there was no association. In one of the positive prostate cancer studies, the authors advised that their findings "should be interpreted cautiously" because of high correlations in the study between the intakes of calcium and phosphorus, between these intakes and dairy consumption, and between phosphorus intake and meat consumption. In the other study, the authors considered the main finding to be a relationship between calcium intake and prostate cancer risk, a relationship that they considered might be modulated by phosphorus intake.

In some areas, however, the findings of studies were in agreement. For example, exposures to higher quantities of dietary phosphorus were associated with potentially adverse physiological outcomes that included changes in serum parathyroid hormone and fibroblast growth factor 23 (FGF 23) concentrations in the 5 studies that investigated these relationships. In 4 other studies, higher dietary phosphorus intake was associated with potentially beneficial changes in biomarkers of bone metabolism, primarily in children. However, most of these studies were observational, few causal connections could be inferred, and, in the studies generating the data, differences in morbidity or mortality were not investigated.

The chief line of argument pursued in the white paper is summarized in the following points, (a) through (j). For the purposes of this summary, primary research studies included in the white paper that examined directly causal or noncausal associations between dietary food-additive phosphorus or total dietary phosphorus intake and morbidity or mortality are designated "Type 1" studies; all other primary research studies included in the white paper are designated "Type 2" studies.

(a) The number of Type 1 studies directly examining dietary food-additive phosphorus was very small: only 2 such studies were identified.
(b) Only Type 1 studies could (even in principle) directly support or refute the safety or otherwise of different intakes of dietary food-additive phosphorus or total dietary phosphorus.
(c) Reliance on Type 2 studies, each taken on its own or considered in combinations, to draw conclusions about the safety or otherwise of different levels of dietary food-additive phosphorus or total dietary phosphorus intake would have been flawed.
(d) Therefore, conclusions drawn in the white paper had to rest primarily on examination of Type 1 studies.
(e) Although Type 1 studies could, in principle, have supported or refuted the safety or otherwise of different intakes of dietary food-additive phosphorus or total dietary phosphorus, in fact, these studies had important methodological limitations.

(f) No Type 1 study was interventional and, therefore, the causality of any associations identified in these studies could not be determined.
(g) The total number of Type 1 studies was small (22 [20%]).
(h) The number of Type 1 studies within each clinical area was even smaller.
(i) Type 1 studies often had contrary results even within single clinical areas.
(j) Limitations of the data available precluded the assessment of net clinical harms or benefits across the clinical areas covered by Type 1 studies.

These and other supporting considerations prevented the drawing of firm conclusions about the safety and possible risks of food-additive phosphate in the general population. This outcome is consonant with the overall assessments of authoritative institutions that have concluded that available data are insufficient to make the required determinations. These institutions include the National Academy of Medicine (formerly, the United States Institute of Medicine) and the European Food Safety Authority (EFSA); the latter will reevaluate the use of phosphates as food additives with high priority by December 31, 2018.

Despite the inadequacy of the evidence currently available, many of the authors of the publications reviewed for the white paper expressed concerns about the quantities of phosphorus and food-additive phosphate in the diets of the populations and subpopulations they studied, and these concerns have been noted by the authoritative bodies cited above. At the same time, most of these authors offered only qualified conclusions and expressed themselves tentatively. In addition, authors of primary research publications, authors of review articles, and authoritative institutions have called for the conduct of further research.

Introduction and Background

Introduction

Phosphorus is integral to many central metabolic processes and is an essential constituent of anatomical structure. It is involved in the cell energy cycle in the form of adenosine triphosphate, in signaling pathways in the form of cyclic monophosphates, in cellular regulation through phosphorylation, and in acid base balance in the form of inorganic phosphate. Phosphorus is found in phospholipids as a major component of all cell membranes, in hydroxyapatite in bones and teeth, and in ribonucleic and deoxyribonucleic acids (European Food Safety Authority 2015).

The forms in which phosphorus occurs in the body may be categorized into 2 groups: inorganic phosphates (uncomplexed dihydrogen and monohydrogen phosphate) and organic phosphates (in which phosphate is a component of proteins, lipids, or carbohydrates). The pool of inorganic phosphate is small, but is the immediate destination of all absorbed phosphate and the primary source from which cells draw phosphate. Organic phosphates are hydrolyzed into inorganic forms before absorption. The inorganic plasma phosphorus concentration is closely controlled through hormonal and other regulation of phosphate absorption from the gut, resorption from and uptake into bone, and (mainly) renal elimination (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board – Institute of Medicine 1997).

Dietary intake of phosphorus (in the form of organic and inorganic phosphates) is essential to human health. Phosphates are ubiquitous and abundant in almost all diets. Major sources of organic phosphates in the diet include protein, both of animal and vegetable origin. Milk, other dairy products, and meat are often important sources of phosphates. Inorganic phosphates are derived mainly from food additives. States of phosphorus deficiency are rare in the general population, "near total starvation" is required to produce dietary deficiency, and deficiency is most commonly limited to certain acute medical states (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board – Institute of Medicine 1997; Otten and others 2006)

Food-grade phosphates are used as additives in food production to function as buffers, sequestrants, acidulants, bases, flavors, cryoprotectants, gel accelerants, dispersants, nutrients, or precipitants, as well as to function as free-flow or ion-exchange agents. Food-grade phosphates are used to chemically leaven cakes, cookies, pancakes, waffles, and donuts; to maintain the structure and hydration of meat, poultry, and seafood products; to improve fluidity of evaporated milk; flavor or add minerals to beverages; and to maintain the structure of canned fruit and vegetable products (Lampila 2013). Phosphates are often the most efficient ingredients to provide the required functionality in these applications, and in some cases, there are not effective and approved alternatives (Fuhrman 2015). Some food-additive phosphates contain minerals other than phosphate (such as calcium, potassium, and magnesium) that are consumed by some populations in quantities below those recommended in guidelines (U.S. Dept. of Health and Human Services, U.S. Dept. of Agriculture 2015).

This white paper presents the outcome of a literature review focused on identifying evidence regarding the association of food-additive phosphate intake with human health. An extensive search identified only 2 primary research publications that focused on data potentially specific to a direct association between a phosphorus food additive and a clinical outcome. This result is consonant with the outcome of a literature search (Eeuwijk and others 2013) performed for the European Food Safety Authority (EFSA) and with EFSA's conclusion in 2005 that "available data were not sufficient to establish a Tolerable Upper Intake Level (UL) for phosphorus" (European Food Safety Authority 2005). This conclusion is cited without modification in EFSA's 2015 Scientific Opinion on dietary reference values for phosphorus (European Food Safety Authority 2015).

For this reason, the vast majority of primary research publications included in this white paper literature review present data relating only to intermediate linkages in chains of effects or non-causal association reaching from dietary food-additive phosphate intake to human health, morbidity, or mortality. Links in such chains may include the following: dietary food-additive phosphate intake; total dietary intake of phosphorus; phosphorus absorption and excretion; serum phosphorus concentration; hormonal or physiological changes; changes in target organ function and biomarkers; and morbidity and mortality.

The review strategy, described in Appendix B1, involved evaluating primary research articles published from 1995 to January 2016 and categorizing the studies according to the chain linkages they examined; analyses are presented according to these categories in Sections "Dietary phosphorus and serum phosphorus concentration" through "Other associations and analysis". In addition, data relevant to certain population subgroups defined by age or disease are examined in Appendix A1. Data from a publication may be relevant to more than one section and may be cited and discussed in several sections. An overview of selected review articles and opinion pieces is provided in Section "Review Articles, Expert Opinion, and Commentary". Finally, an overall summary of the data is presented (Section "Summary"), and conclusions are presented (Section "Overall Conclusions").

Table 1–Article count by category.

Article count by category[a,b]	Dietary food-additive phosphate content	Total phosphorus content in diet	Load of ingested phosphorus[c]	Phosphorus balance[d]	Change in serum phosphorus[e]	Physiological outcomes	Target organ effects/ biomarkers	Clinical outcomes	Totals
Dietary food-additive phosphate content	0	0	0	0	3	3	3	2	11
Total phosphorus content in diet		10	0	0	2	11	12	20	55
Load of ingested phosphorus[c]			0	0	0	21	1	0	22
Phosphorus balance[d]				0	1	0	1	1	3
Change in serum phosphorus[e]					0	1	3	15	19
Physiological outcomes						0	0	0	0
Target organ effects/biomarkers							0	0	0
Clinical outcomes								0	0
Grand total									110

[a]Counts are based on the classification of articles as displayed by category in the master clinical table. The counts include 4 primary research articles (those by Lynch and others (2011), Noori and others (2010a), Newsome and others (2013), and Waller and others (2007) that are not included in the master clinical table but receive their main treatments in the appendices.
[b]Cells along the main diagonal count studies in which only the indicated link has been assessed (and no linkage to other links).
[c]Including phosphorus supplementation.
[d]Including phosphorus absorption and excretion.
[e]Including change in tissue phosphorus and salivary phosphorus.

Primary research publications included in the review are listed in the master clinical table (Table D1, Appendix D) by chain linkage. For each publication, the table presents a summary of study design and results, as well as a methodological quality rating. The rating process in this white paper was broadly informed by the U.S. Food and Drug Administration (FDA) guidance for industry on an evidence-based review system (FDA 2009), and the rating categories used are defined in Appendix C.

Of the studies included in the white paper that examined various associations of dietary food-additive phosphorus, very few specified which compounds were under investigation as additives. The (usually implicit) assumption in the studies was that changes in total dietary phosphorus intake or absorption resulting from the inclusion of food-additive phosphorus in the diet were central to the investigation and not the specific phosphorus additive(s) ingested.

The chief line of argument pursued in the white paper is summarized in the following points, (a) through (m). For the purposes of this summary, primary research studies included in the white paper that examined directly causal or noncausal associations between dietary food-additive phosphorus or total dietary phosphorus intake and morbidity or mortality are designated "Type 1" studies; all other primary research studies included in the white paper are designated "Type 2" studies.

(a) The number of Type 1 studies directly examining dietary food-additive phosphorus was very small: only 2 such studies were identified.
(This point is discussed and presented in Section "Phosphate Food Additives and Human Health", including in Table 1). Therefore, such studies are discussed and analyzed together with studies examining total dietary phosphorus intake. The contribution that food-additive phosphorus makes to total dietary phosphorus is discussed in several places (for example, in Section "Use of phosphate food additives").

(b) Only Type 1 studies could (even in principle) directly support or refute the safety or otherwise of different intakes of dietary food-additive phosphorus or total dietary phosphorus. (This point is argued in Section "Direct and Indirect Evidence").

(c) Reliance on Type 2 studies, each taken on its own or considered in combinations, to draw conclusions about the safety or otherwise of different levels of dietary food additive phosphorus or total dietary phosphorus intake would have been flawed. (This point is argued in Section "Direct and indirect evidence").

(d) Therefore, conclusions drawn in the white paper had to rest primarily on examination of Type 1 studies.

(e) Although Type 1 studies could, in principle, have supported or refuted the safety or otherwise of different intakes of dietary food additive phosphorus or total dietary phosphorus, in fact, these studies had important methodological limitations. (Limitations are listed and discussed in general in Sections "Interventional versus observational studies and other study design factors" through "Endpoint ascertainment"; and as they apply to Type 1 studies, in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes").

(f) No Type 1 study was interventional and, therefore, the causality of any associations identified in these studies could not be determined. (This point is discussed in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes").

(g) The total number of Type 1 studies was small (22 [20% of all primary research studies reviewed]). (This point is discussed in Section "Phosphate Food Additives and Human Health").

(h) The number of Type 1 studies within each clinical area was even smaller. (This point is discussed in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes").

(i) Type 1 studies often had heterogeneous designs and contrary results even within single clinical areas. (This point is discussed in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes").

(j) Limitations of the data available precluded the assessment of net clinical harms or benefits across the clinical areas covered by Type 1 studies. (This point is stated in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes").

(k) Points (e) through (j) prevented the drawing of firm conclusions about the safety and possible risks of food-additive phosphate in the general population. (This result is indicated in Section "Overall Conclusions").

(l) This result is supported by referring to the fact that similar conclusions were reached by certain authoritative institutions. (This is indicated in Section "Overall Conclusions").
(m) Finally, attention is drawn to the reevaluation by EFSA of the use of phosphates as food additives with high priority by December 31, 2018. (This is indicated in Section "Overall Conclusions").

Dietary sources and metabolism of phosphate

Sources of dietary phosphate. There are 2 types of phosphorus in food: natural (or organic) and added (or inorganic). Natural sources of phosphorus are dependent on enzymatic digestion or degradation to release phosphate from organic compounds. As a result, phosphorus from natural sources is slowly and less efficiently absorbed. Inorganic phosphates are added to food during preparation or processing. They are primarily added as inorganic phosphate salts that rapidly dissociate in stomach acid, requiring no enzymatic digestion. Inorganic phosphates are rapidly and efficiently absorbed (Otten and others 2006; Noori and others 2010b).

Naturally occurring phosphates. Many foods naturally contain high levels of phosphorus. These include yogurt, cottage cheese, eggs, fresh meat and poultry, fish, legumes, nuts, seeds, beer, and wine. Foods with low or medium quantities of natural phosphorus (NP) include nonprocessed milk, oats, rice, semolina, most vegetables, potatoes, butter, margarine, oils, tea, and coffee (Moore and others 2015). In plants, phytate is the primary storage form of phosphorus. Phosphate in the form of phytates is not directly available to humans and is generally poorly absorbed: its absorption requires the action of phytases, found in some foods, in colonic bacteria, and in yeasts (Otten and others 2006).

Phosphate food additives: definition and uses. Definition of food-additive phosphate Food additives are defined by FDA in 21 United States Code 321, Paragraph (s), as follows:

The term 'food additive' means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include (1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or (2) a pesticide chemical; or (3) a color additive; or (4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 U.S.C. 451 et seq.] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 U.S.C. 601 et seq.]; (5) a new animal drug; or (6) an ingredient described in paragraph (ff) [of U.S.C. 321] in, or intended for use in, a dietary supplement.

The purpose of this definition is clarified by FDA as follows (International Food Information Council Foundation, US FDA 2010):

The purpose of the legal definition, however, is to impose a premarket approval requirement. Therefore, this definition excludes ingredients whose use is generally recognized as safe (GRAS; where government approval is not needed), those ingredients approved for use by the FDA or the U.S. Department of Agriculture prior to the food additives provisions of law, and color additives and pesticides where other legal premarket approval requirements apply.

The FDA's definition of food additives thus excludes substances generally recognized as safe (GRAS) by FDA. Eight different phosphate salts commonly used as food additives, as well as phosphoric acid, are so recognized and thus are excluded by the definition: these are tabulated by Kalantar-Zadeh and others (2010). Very few of the primary research publications reviewed for the white paper that examine possible associations, whether direct or indirect, of phosphate food additives with health, morbidity, or mortality specify which phosphate compounds are being investigated; nevertheless, all these compounds would be expected to appear on the FDA list of GRAS substances. To this extent, the FDA definition for food additives could not be used to determine which publications to include in the white paper review.

The European Commission defines food additives as follows (Article 1(2) of Directive 89/107/EEC):

For the purposes of this Directive 'food additive' means any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of such food results, or may be reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such foods.

The European Commission definition has the advantage of not excluding GRAS substances; nevertheless, neither this definition nor the FDA definition was used in determining the contents of the white paper. Such regulatory definitions informed the critical review only indirectly. Instead, the subject matter of the white paper was determined by primary research publications selected from PubMed literature searches that included "food additive" and "additive(s)" as key terms in search strings. The literature search and selection strategy used for the white paper is described in Appendix B1.

White paper usage of the term "phosphate food additives". In this white paper the term "phosphate food additives" and similar terms are sometimes used to include phosphoric acid: this is apparent from the contexts in which the terms are used. In other places, where such usage could result in misconstruction or would be otherwise inappropriate, joint reference is made explicit by using phrases such as "food-additive phosphates or phosphoric acid" or reference is made to phosphoric acid only.

Uses of phosphate food additives. Food-grade phosphates are used as additives in food production to function as buffers, sequestrants, acidulants, bases, flavors, cryoprotectants, gel accelerants, dispersants, nutrients, or precipitants, as well as to function as free-flow or ion-exchange agents. Food-grade phosphates are used to chemically leaven cakes, cookies, pancakes, waffles, and donuts; to maintain the structure and hydration of meat, poultry, and seafood products; to improve fluidity of evaporated milk; flavor or add minerals to beverages; and to maintain the structure of canned fruit and vegetable products (Lampila 2013). Phosphates are often the most efficient ingredients to provide the required functionality in these applications, and in some cases, there are not effective and

approved alternatives (Fuhrman 2015). Some food-additive phosphates contain minerals other than phosphate (such as calcium, potassium, and magnesium) that are consumed by some populations in quantities below those recommended in guidelines (U.S. Department of Health and Human Services, U.S. Department of Agriculture 2015).

Many different phosphate salts are used as food additives, and the absorption of this inorganic phosphate depends on the mineral components of the salts in which it is contained (Calvo and others 2014). More-processed foodstuffs generally contain more inorganic phosphate than the less-processed equivalents, and substitution of highly processed foods for minimally processed foods in a characteristic U.S. diet may increase phosphorus content by approximately 60% (some 600 mg/d) (Carrigan and others 2014).

Food-grade phosphates indirectly contact food when they are used in sanitizers, packaging materials, adhesives and coatings, lubricants, food contact polymers, and scale remover in dairy and beer facilities. Food processing aids also contain food-grade phosphates (Lampila 2013).

Overview of phosphate metabolism. Phosphates are central for cardiovascular and neuromuscular function, bone development, and enzyme-mediated and cellular signaling processes. These are discussed in Section "Introduction". Serum phosphate levels are maintained by intestinal phosphate absorption, renal phosphate handling, and exchange of phosphate in extracellular fluid with that in bone and intracellular fluid. Hormones such as parathyroid hormone (PTH), 1,25 dihydroxyvitamin D [1,25$(OH)_2$D], FGF-23, and Klotho regulate serum phosphate levels by modulating intestinal phosphate absorption, renal phosphate reabsorption, and bone metabolism. Phosphorus homeostasis is intricately linked to that of calcium because of the actions of calcium-regulating hormones, such as PTH and 1,25$(OH)_2$D, at the level of the bone, the gut, and the kidneys. The molar ratio of calcium to phosphorus in the adult body is approximately 1.37:1 to 1.55:1 (European Food Safety Authority 2015). To maintain phosphate balance in healthy adults, an equivalent amount of phosphate is generally absorbed by the intestine and excreted into urine; during pregnancy, lactation, and growth in children, phosphorus intake exceeds excretion. The molecular mechanisms regulating this balance are unclear (Fukumoto 2014). Calcium and phosphate serum levels are maintained in a tightly regulated homeostasis, often referred to as calcium-phosphate balance. The hormones that regulate serum phosphate levels (PTH, 1,25D, and FGF-23) also regulate serum calcium. These hormones form a feedback loop in which PTH and 1,25$(OH)_2$D stimulate FGF-23 secretion and FGF-23 negatively regulates 1,25$(OH)_2$D production (Evenepoel and Wolf 2013). Additionally, several studies have shown a circadian pattern of serum phosphate (Becker and others 2009; Moe and others 2011; Ix and others 2014). Phosphate levels peak between 02:00 am and 04:00 am and reach their nadir between 08:00 am and 10:00 am. Intestinal phosphate absorption is known to contribute to circadian changes in serum phosphate; however, the mechanism of this circadian rhythm is unclear.

Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies

The literature review revealed apparent disagreement about the safety of phosphate food additives. Several authors expressed concerns about the large quantity of phosphorus in the characteristic diets of healthy populations (Ritz and others 2012; Gutierrez 2013; Chang and others 2014); many of these authors qualified their concerns by noting the need for further investigation. Some authoritative bodies, however, have established tolerable upper intake levels (ULs) for phosphorus that are considerably above the intakes of the vast majority of people (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board – Institute of Medicine 1997; Otten and others 2006), whereas others have determined that there is insufficient evidence for setting such levels. EFSA concluded in 2005 that "available data are not sufficient to establish an UL for phosphorus" (European Food Safety Authority 2005). This conclusion is cited without modification in EFSA's 2015 Scientific Opinion (European Food Safety Authority 2015).

Several systematic methodological difficulties may underlie this disagreement and many constitute broadly applicable limitations on the quality of the evidence offered by the studies reviewed in this white paper. Some of the methodological difficulties, including factors that underlie the paucity of direct evidence of causation and the difficulty in obtaining even indirect high-quality evidence of causal or noncausal associations, are listed and discussed briefly in the following subsections (Sections "Direct and indirect evidence" through "Endpoint ascertainment"). Most of the primary publications cited are reviewed in other sections of the white paper. The FDA Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims (SEHC) contains a general list of factors affecting the quality of dietary studies, many of which are applicable here (FDA 2009). Many of these factors are discussed also by Lichtenstein and others (2008).

Direct and indirect evidence. The literature search and selection yielded only 2 primary research publications that focused on data potentially specific to the direct association of a phosphorus food additive with a clinical outcome; an additional 20 publications examined the clinical associations of total dietary phosphorus intake.[1] All the other publications included in the white paper examined only intermediate links in putative chains of effects and associations linking dietary phosphorus intake with morbidity or mortality. Concatenation of these intermediate links may suggest associations of dietary phosphorus intake with morbidity or mortality and indicate possible directions for further research. In addition, some persuasive pathophysiological models have been proposed that could support such associations. However, indirect inference cannot be substituted for data from studies directly addressing the presence or absence of an association between dietary phosphorus intake and morbidity or mortality (a methodological point made also by Herrington (Herrington and Howard 2003), in the context of cardiovascular disease [CVD] and hormone replacement therapy [HRT]). Further illustrations of these points include the following:

- The paucity of direct evidence (as well as the limitations of indirect evidence) is corroborated by statements in several publications reviewed for the white paper. Two examples are the following:
  - Murtaugh and others (2012), in their paper reporting a study examining the association between total dietary phosphorus intake and mortality in persons with moderate chronic kidney disease (CKD), stated the following:
    - Taken together, [indirect evidence] could be interpreted as evidence that high dietary phosphorus

[1]Three additional publications reporting trials of phosphate-fortified chewing gum on dental staining were considered beyond the scope of this white paper.

intake could be deleterious in those with moderate kidney disease. However, to our knowledge, there are no [previously] published data on whether high dietary phosphorus intake is indeed associated with increased mortality in moderate CKD.

-Gutiérrez noted "the scarcity of epidemiologic data associating excess dietary phosphorus consumption itself (and not surrogate markers such as serum phosphorus) with adverse cardiovascular outcomes" (Gutiérrez and others 2012).

- The findings of "direct" associations in observational studies may be contrary to the outcomes of interventional trials addressing the same question (FDA 2009).

Interventional compared with observational studies and other study design factors. Of the 110 primary research publications identified for inclusion in this white paper, 71 (65%) report observational studies, and 36 (33%) report interventional studies. Of the 22 publications directly examining associations between dietary phosphorus and morbidity or mortality, none report an interventional study. On the one hand, observational studies, by their very nature, cannot provide evidence of causal relationships (FDA 2009); on the other hand, designing and executing interventional trials of adequate duration (possibly several years) and size to examine effects of relevant dietary interventions on clinical outcomes are likely to be logistically complicated and expensive. Illustrations of these points include the following:

- Analysis of results from observational studies requires meticulous control for confounding variables and is subject to bias by unrecognized confounders (FDA 2009); extensive lists of acknowledged confounders in investigations of dietary phosphorus are provided in Table 9. Conversely, Noori and others (2010a) discuss "overadjusted" statistical models and favor a model incorporating only an intermediate number of adjustments; however, because of uncertainty about the "best" model, they report 4 analyses using different levels of adjustment. Bansal and others (2013) determined that postmenopausal women on HRT had a mean serum phosphorus concentration that was 4.4% lower than those not receiving replacement therapy: an implication of this finding is that studies of serum phosphorus concentration that enroll postmenopausal women and do not control for use of HRT may have biased outcomes. The relative strengths and weaknesses of the various types of observational studies, including prospective compared with retrospective studies, and cohort, case–control, and cross-sectional studies are well recognized (FDA 2009).
- Clinical effects or noncausal clinical associations of differing dietary intakes of phosphorus may take many years to manifest (Wilson and others 2015). Although surrogate endpoints have been examined in many studies instead of mortality and morbidity (Houston and others 2013) and allow shorter study durations, validation of the surrogates and their generalizability to different clinical settings (including the healthy population) have been problematic (based on SEHC).
- Subjects' phosphorus intakes in different studies may be grouped into tertiles, quartiles, or quintiles. Furthermore, the cutoffs, even for quantiles of the same type, may differ across studies: the broader implications of relative risk (RR) across categories may therefore differ across studies, and integration, interpretation, and generalization of findings may consequently be difficult. For example, in the prostate cancer study reported by Wilson and others (2015), quintiles of dietary phosphorus intake are characterized by means, and the mean intake was 1783 mg/d for the highest quintile; in contrast, however, in the study in colon cancer reported by Boutron and others (1996), male subjects in the highest quintile all had phosphorus intakes greater than 2038 mg/d.
- Interpretation of studies performed in the past, as well as integration of findings across studies performed years apart, is complicated by population-level changes in dietary phosphorus intake. In the United States, there has probably been a progressive increase in the phosphorus content of food due largely to an increase in food additives in processed food (Otten and others 2006; Noori and others 2010b).

External validity of studies. Several factors may limit the generalizability of study results. Examples include the following:

- The use of findings from studies in diseased subpopulations, especially those with diseases such as CKD, to draw conclusions regarding the general healthy population, may be unwarranted and require substantiation. Similar considerations apply to subpopulations defined by age, sex, or race. Even the applicability of epidemiological results from healthy subpopulations constituting convenience samples to the general healthy population is a matter of the investigators' judgment (St Sauver and others 2012).
- The use of findings from studies that manipulate phosphorus intake through the administration of phosphorus supplements (or the implementation of other short-term dietary alterations) to draw conclusions about the effects of habitual diets that differ in phosphorus content may be unwarranted and require substantiation. Some short-term interventional phosphorus loading studies have differed in their outcomes from longer-term studies (European Food Safety Authority 2015).
- The use of findings from studies in one country to draw conclusions about populations in others may be unwarranted and require substantiation. This is discussed further in Section "Composition of foods and diets".
- The use of findings from studies conducted in the past to draw conclusions about current populations may be unwarranted and require substantiation, in part, because of possible changes in food composition over time (Otten and others 2006; Noori and others 2010b).

Quantification of dietary phosphorus. There are many well-recognized difficulties in adequately quantifying dietary intakes (Shim and others 2014), and many of these may be particularly acute in the case of food-additive phosphates and organic phosphates, in part because of the ubiquity of these substances in the diet. Difficulties include the following:

- Tewnty-four-hour dietary recall, dietary records, dietary history, food frequency questionnaires (FFQs), and other tools are employed in many of the studies examined in the white paper. Table 9 lists the dietary ascertainment methods for all studies included in the white paper that directly examine associations between dietary intakes of phosphorus and morbidity or mortality. The limitations of these methods and instruments are numerous and significant (Poslusna and others 2009; Shim and others 2014) and are discussed in many of the publications reporting these studies (discussion by Elmståhl

and others 1998 and Merritt and others 2015). Limitations include, but are not limited to, the following:

  – Reporting bias, in methods relying on contemporaneous dietary records
  – Recall bias, introduced by subject or interviewer, in methods relying on retrospective assessment of food consumption
  – Changes in the diets of subjects over time in studies assessing diet only at sparse discrete time points, for example, at study entry only
  – Systematic misreporting, for example, in methods relying on portion size: overweight subjects may tend to underreport portion size (FDA 2009)
  – Systematic exclusion of dietary components, in methods using closed as opposed to open-ended questionnaires
  – Failure to account for cooking methods (FDA 2009), which may alter the amount of phosphorus available for absorption (Delgado-Andrade and others 2011)
  – Failure to account adequately for dietary components which may be displaced by higher intakes of other components (Heaney and Rafferty 2001; FDA 2009)

- The type of questionnaire chosen may have an important effect on the conclusions that can be drawn from the results of a study and, consequently, on the recommendations that can be made based on the study. Publications selected for inclusion in the white paper review differ widely in the degree of detail of the diet ascertainment methods used (Noori and others 2010a; Ramezani Tehrani and others 2013).
- Nutrient composition tables used to calculate phosphorus intake based on the estimated intakes of various foods may be out-of-date or otherwise inaccurate. Inaccuracies may differ systematically by type of foodstuff (for example, vegetable compared with meat sources) (Moe and others 2011). The progressive increase in the prevalence of processed foods in the diet may result in systematic underestimation of phosphorus intake (Sullivan and others 2007; Murtaugh and others 2012; Calvo and others 2014; Chang and others 2014). The contributions of food-additive phosphate to total dietary phosphorus intake cannot be reliably distinguished from those of protein-based organic phosphate (Kalantar-Zadeh and others 2010).

Publications included in the white paper that report studies of the phosphorus content of food are reported in Section "Phosphorus content in food".

Quantification of absorbed phosphorus. The fraction of ingested phosphorus that is absorbed varies widely and is affected by several factors. In 2015, EFSA concluded that the amount of phosphorus in the diet available for absorption cannot be determined (European Food Safety Authority 2015). Difficulties that have been noted in quantifying dietary phosphorus absorption include the following:

- The absorption of phosphorus occurs by both passive diffusion and active transport. The latter is under hormonal control, notably by PTH and vitamin D. Fractional absorption in adults may range from 55% to 80% (European Food Safety Authority 2015).
- Inorganic phosphates in food additives are absorbed more readily and completely (80% to 100%) than organic phosphates because their absorption does not require prior enzymatic hydrolysis. The forms in which organic phosphate is ingested markedly affect its availability for absorption. Phosphate from vegetable sources is in the form of phytates and is poorly absorbed (in the absence of pretreatment of the foodstuff with phytases). Phosphate from animal sources is far better absorbed (Kalantar-Zadeh and others 2010; Noori and others 2010b).
- The absorption of inorganic phosphates in food additives depends on the mineral component of the salts in which they are contained. Eight different phosphate salts commonly used as additives, as well as phosphoric acid, are classified as GRAS and are tabulated by Kalantar-Zadeh and others (2010). Over 20 different phosphate salts are included in the list of food additives permitted in the European Union (European Food Safety Authority 2013). Phosphoric acid, an additive used in colas, is 100% bioavailable and very readily absorbed.
- Conutrients influence the fraction of ingested phosphorus that is absorbed and are discussed in Section "Effects of conutrients".

Effects of conutrients. Conutrients influence the outcomes of studies, the interpretations of these outcomes, and the resulting recommendations in several ways:

- Conutrients, notably calcium, affect the absorption of phosphorus. Ingested calcium binds phosphorus in the gut, thereby preventing absorption. In addition, unabsorbed calcium prevents the hydrolysis of phytates by gut bacteria, thereby preventing the release of phosphate for absorption. Certain medications, such as aluminum-containing antacids, decrease phosphate absorption (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and Nutrition Board – Institute of Medicine 1997).
- Separating possible effects and associations of phosphorus intake from those of some other nutrients, notably calcium, are complicated by their co-occurrence in foodstuffs: for example, dairy products may constitute the chief sources of both calcium and phosphorus. This is a concern expressed in many publications reporting studies of morbidity or mortality. For example, Wilson and others (2015) include the following caveat in the concluding paragraph of their report on prostate cancer risk: "Given the high correlation between calcium and phosphorus intake, as well as their correlation with dairy and meat (for phosphorus) intake, our findings should be interpreted cautiously." Merritt and others (2015) express similar concerns. Karp and others (2013) determined that phosphate in cheese caused greater acute increases in serum phosphate concentrations than phosphate in other dietary sources.
- The calcium-to-phosphorus ratio in ingested food may be significant independent of the quantity of either mineral alone (Lin and others 2014; European Food Safety Authority 2015). Several studies report on possible associations of this ratio (Boutron and others 1996; Kesse and others 2005).
- Studies designed to contribute to the evolution of pragmatic recommendations about diet must take into account that dietary adjustments aimed at changing phosphorus intake will also affect intakes of other nutrients. Murtaugh and others (2012) discuss the tradeoff between decreasing phosphate intake and jeopardizing overall nutritional status in patients with CKD (Murtaugh and others 2012).
- Nutrients in foods other than those that were the focus of reports discussed in this white paper may contribute to or be the

sole cause of study outcomes (Kesse and others 2006), and apparent associations, for example, with phosphorus intake, may be spurious. A report on the evaluation of the safety of (unprocessed) red meat and processed meat prepared by the World Health Organization International Agency for Research on Cancer states that the Agency determined that there is "sufficient evidence" of the carcinogenicity of processed meat. Processed meat has been recognized as being rich in phosphate food additives (Carrigan and others 2014). However, the report does not mention food additives or phosphates, and discusses the formation of carcinogenic N-nitroso-compounds during food processing (Bouvard 2015).

Composition of foods and diets. The composition of various foodstuffs, the proportions of the diet they constitute, and the combinations in which they are characteristically consumed differ between countries. These differences may account for contrary outcomes in studies conducted in different countries, as well as complicate the synthesis of data across studies (Tavani and others 2005; Kesse and others 2006).

Serum phosphorus concentration as a surrogate for dietary intake. The literature search performed for the white paper targeted the various health associations of dietary phosphorus intake. Despite this focus, a substantial proportion (15 of 38, 39%) of the primary research publications that investigated associations of phosphorus with morbidity and mortality examined serum phosphorus concentration rather than dietary phosphorus intake. However, the use of serum phosphorus concentration as a proxy for dietary phosphorus intake may not be appropriate because of several factors:

- Serum phosphorus concentration is subject to significant diurnal variation and short-term fluctuation in relation to meals. Studies have not always taken these factors into account (Murtaugh and others 2012; Chang and others 2014). Multiple measurements at different times of day may be required if serum phosphorus concentration is to be used as a surrogate for dietary phosphorus intake (European Food Safety Authority 2015).
- Furthermore, in persons with normal renal function, homeostatic mechanisms generally maintain serum phosphorus concentrations within narrow limits despite wide fluctuations in dietary phosphorus intake (European Food Safety Authority 2015). These mechanisms fail as renal function declines, and serum phosphorus concentrations are more directly associated with dietary intake in more advanced stages of CKD (Murtaugh and others 2012).
- Excessive dietary phosphorus intake may have adverse clinical consequences without leading to elevations of serum phosphorus concentration (Chang and others 2014).
- Only a small fraction of total body phosphorus is found in the plasma, and serum phosphorus concentration is not an adequate indicator of phosphorus status in other compartments, again because of very effective homeostatic mechanisms.

Other surrogates and biomarkers. Other mediators of the physiological and pathophysiological effects of phosphate have been proposed as surrogates of dietary phosphorus intake or biomarkers of clinically significant consequences of excessive intake.

For example, in 2013, Gutiérrez proposed FGF-23 and Klotho as such markers (Gutierrez 2013). However, a report by Houston and others (2013) in the same year notes an absence in the study population (patients with CKD not yet requiring hemodialysis) of any significant association between FGF-23 and dietary phosphorus intake. In a 2015 publication, EFSA concluded there were insufficient data to support the use of FGF-23 as a marker of phosphorus status (European Food Safety Authority 2015).

Endpoint ascertainment. Ascertainment of endpoints may present substantial challenges. For example, long study durations may be needed to accumulate sufficient endpoints (such as deaths) in prospective investigations, and the use of surrogate endpoints may weaken conclusions. These points are discussed briefly in Section "Interventional versus observational studies and other study design factors", Section "Serum phosphorus concentration as a surrogate for dietary intake", and Section "Other surrogates and biomarkers".

Phosphate Food Additives and Human Health

An extensive search identified only 2 primary research publications that focused on data potentially specific to a direct association between a dietary phosphorus food-additive (specifically, in the form of phosphoric acid) and a clinical outcome. The remaining articles present data relating only to intermediate linkages in chains of effects or noncausal associations reaching from dietary food-additive phosphate intake to human morbidity or mortality (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board - Institute of Medicine 1997). The various causal and noncausal associations examined by primary research publications were used to classify them for review in the white paper, and Table 1 displays counts of articles according to this classification.

A total of 110 primary research articles were included in the white paper review. Only 11 (10%) of these articles focused on various associations specifically of dietary food-additive phosphorus (top row of Table 1), and only 2 (2%) of these examined its associations with clinical outcomes. Half of the articles (55 [50%]) focused on various associations of the total phosphorus (TP) content in the diet (2nd row of Table 1). Of these, 20 (18%) focused on associations of total dietary phosphorus with clinical outcomes. A further 21 (19%) examined the association of the load of ingested phosphorus with physiological outcomes, and these articles constituted the largest category. Another 10 (9%) of the articles examined aspects of the phosphorus content in the diet without examining associations with other chain links.

Figure 1 displays a count of primary research articles included in the white paper by year of publication. Just under half (49 of 110 [45%]) were published in or after 2010; over three-quarters (82 of 110 [79%]) were published in or after 2005.

The published clinical studies that described the various associations of dietary phosphorus are summarized in Sections "Dietary phosphorus and serum phosphorus concentration" through "Other associations and analyses", which cover the following areas:

- Section "Dietary phosphorus and serum phosphorus concentration": association of serum phosphorus concentrations with dietary food-additive phosphates and association of serum phosphorus concentrations with target organs and biomarkers, physiological outcomes, and clinical outcomes
- Section "Dietary phosphorus, target organs, and biomarkers": association of dietary and food-additive phosphate with target organs and biomarkers
- Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes": association of dietary and food-additive phosphates and phosphorus load with regulatory hormones and physiological outcomes

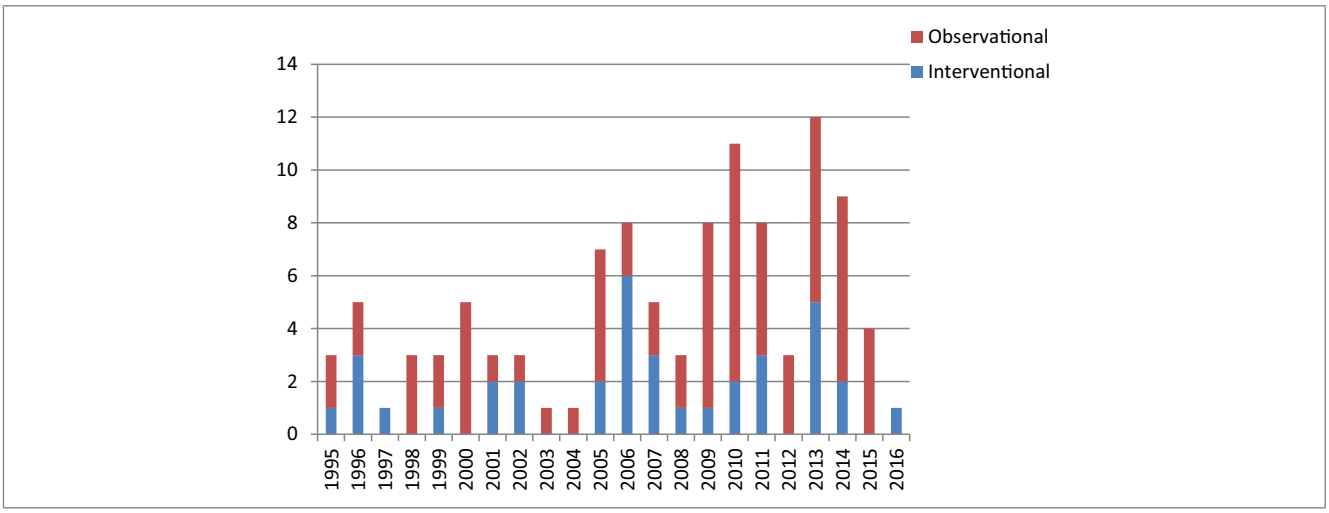

Figure 1–Primary research article count: interventional and observational studies by year of publication.

- Section "Dietary phosphorus and clinical outcomes": association of dietary food-additive phosphates with clinical outcomes
- Section "Other associations and analyses": other associations, including load of ingested phosphorus, and examination of phosphorus content in food

In addition, studies with data specific to certain subpopulations defined by age or disease or increased risk of disease are discussed in Appendix A.1 and Appendix A1.2.

Publications are cited in each section where they contribute to the discussion and are cross-referenced between sections as required. Publication summaries vary in detail and format according to the data they contain, their relevance to the topics under examination, and the requirements of the arguments being presented.

Dietary phosphorus and serum phosphorus concentration

All the studies in this section evaluated the associations between serum phosphorus concentrations and different aspects of dietary phosphorus intake, changes in target organ function or biomarkers, or changes in physiological outcomes. A summary of each study is presented in this section; information is also presented in Appendix D, Table D1, Master Clinical Table.

Food-additive phosphate and serum phosphorus concentration. Only one primary research publication was included in the white paper review that directly assessed the relationship between food-additive phosphate and serum phosphorus concentration as a primary endpoint. Moore and others (2015) conducted a cross-sectional analysis of serum phosphorus concentration in relation to clinical characteristics and dietary intake reported 24 h before blood analysis. Data were extracted from the National Health and Nutrition Examination Survey (NHANES) 2003 to 2006. Of the total 20470 participants, data from 7895 adult participants were analyzed. Analyses were restricted to adults aged 20 to 85 y. Additionally, pregnant women and those with missing information were excluded from the analysis. Fasting blood and urine samples were collected from subjects. Subjects met with trained dietary and health interviewers to provide a detailed history of their diet in the 24 h before sample collection. Many variables had positive and significant associations with serum phosphorus levels. These included being underweight (body mass index [BMI] <18.5), having a low estimated glomerular filtration rate (eGFR) (that is, <30 mL/min/1.73 m^2); 0.8% of participants having an elevated albumin-to-creatinine ratio, having a dietary intake of dairy foods with or without inorganic phosphates added, and having a dietary intake of cereals and grains with inorganic phosphates added. There was no correlation between serum phosphorus concentration and the level of education completed or family income. This study is also discussed in Appendix A1.2.1.3. The conclusions drawn by Moore and others (2015) are correlative. The authors were unable to demonstrate a direct relationship between consumption of food-additive phosphate and serum phosphate levels. Nevertheless, Moore and others concluded that adjusting for kidney disease revealed a dietary component related to the serum phosphorus concentration that is stronger in foods having phosphate additives than those without phosphate additives. Having made this correlative conclusion, it was the authors' opinion that FDA should consider adding phosphorus to the Nutrient Facts Label and that food manufacturers should consider alternatives to phosphate additives.

Total dietary phosphorus and serum phosphorus concentration. Four primary research publications assessed the relationship between total dietary phosphorus and serum phosphorus concentrations. Each study evaluated different aspects of associations of serum phosphorus concentrations with dietary phosphorus intake in different subpopulations. There is no association between the results of each of these 4 studies or between the results of the 4 studies with an overall cause and effect relationship of dietary phosphorus and phosphorus serum levels in the general population. Mataix and others (2006) conducted a cross-sectional survey in Andalusia, Spain, to identify factors associated with the dietary intake and plasma levels of calcium, phosphorus, and magnesium. Nutrient intakes were studied in a random sample of 3421 subjects (1747 men, 1674 women) aged between 25 and 60 y. Blood samples were obtained for biochemical analysis in a random subsample of 354 subjects (170 men, 184 women). Food consumption was assessed by a 48-h recall. Information about level of education, smoking habit, alcohol consumption, and physical exercise was collected with a structured questionnaire. The results indicated that sex, age, educational level, obesity, smoking, alcohol use, and physical activity were associated with differences in nutrient intakes. However, the analysis of blood samples showed no significant correlations between the intakes and plasma levels of phosphorus, calcium, and magnesium. Of note, obese people (BMI ≥ 30 kg/m^2) consumed less calcium, phosphorus, and

magnesium; only plasma calcium concentrations were significantly lower in obese ($P < 0.05$) than in nonobese people (Mataix and others 2006).

Ix and others (2014) conducted a crossover feeding study to determine the circadian pattern of serum phosphate concentrations in subjects with CKD. Since considerable diurnal variations have been observed in serum phosphate concentrations of healthy individuals, it is unknown if similar circadian patterns persist in CKD or if modification of dietary phosphate intake influences the circadian rhythm in individuals with CKD. A total of 11 subjects with CKD (eGFR: 30 to 45 mL/min/1.73 m^2) and 4 healthy control subjects received a high-phosphorus (2500 mg/d), normal-phosphorus (1500 mg/d), and low-phosphorus (1000 mg/d and 1000 mg lanthanum carbonate administered 3 times per day) diet for 5 d followed by a 10-d washout. Dietary phosphorus was provided from natural food sources rather than phosphate supplementation. After each 5-d diet period, serum phosphorus and other measurements were made every 4 h for 24 h. In CKD and healthy subjects who consumed a high-phosphorus diet, serum phosphorus concentrations were consistently lowest at 08:00 (4.2 ± 0.5 mg/dL, CKD) with peaks at 16:00 (4.5 ± 0.8 mg/dL, CKD) and 04:00 (4.4 ± 0.6 mg/dL, CKD). A rapid decline in serum phosphorus concentrations was observed between 04:00 and 08:00 with all 3 diets in CKD and healthy subjects. There was no corresponding increase in urine phosphorus excretion or PTH or FGF-23 concentrations. Overall, a circadian pattern of serum phosphorus concentration was observed in CKD and could be modified by phosphorus intake.

A study evaluated the association of dietary phosphorus with left ventricular mass (LVM) in 4494 subjects with no CVD from the Multi-Ethnic Study of Atherosclerosis (MESA) (Yamamoto and others 2013). The study design is described in Section "Dietary phosphorus, target organs, and biomarkers". The study also evaluated the association between serum phosphorus concentrations and dietary phosphorus in a subset of 947 subjects. The authors indicated that there was no meaningful relationship between estimated dietary phosphorus intake and serum phosphorus concentrations (correlation coefficient: −0.055).

A randomized study evaluated 66 healthy males and females, aged 18 to 45 y, who were randomized to either phosphate-depleted or -loaded diets for 5 d, after a 4-d run-in diet (Burnett and others 2006). On days 1 through 4, the diet contained 77 g of protein, 1000 mg of calcium, and 900 mg of phosphate. On days 5 through 9, the protein content was decreased for both groups to facilitate the decrease in dietary phosphate in the phosphate-depleted group that consisted of 500 mg phosphate and the phosphate-depleted group received 2.2 g of aluminum and magnesium hydroxide 4 times a day with meals to decrease absorption of dietary phosphate. The phosphate-loaded group received phosphate supplements (either Neutra-Phos or Phos-NaK) 4 times a day with meals for 5 d such that the total daily phosphate intake was 2500 mg (500 mg from the diet and 2000 mg from the supplements). The results demonstrated that serum phosphorus levels were significantly reduced after phosphate deprivation but there were no differences in serum phosphorus levels after dietary phosphate loading (Burnett and others 2006). Overall, evidence suggests that reducing phosphate intake reduces serum phosphate levels. However, there is not enough evidence to determine the effects of phosphate loading on serum phosphate.

In summary, the results from 3 studies evaluated distinct aspects of associations of serum phosphorus concentrations with dietary phosphorus intake in different subpopulations. One study showed no significant correlations between the intakes and plasma levels of phosphorus, calcium, and magnesium in 3421 healthy adults. Another study determined that there was a circadian pattern of serum phosphorus concentration in individuals with CKD and that the serum phosphorus concentrations could be modified by phosphorus intake. A 3rd study demonstrated that serum phosphorus levels were significantly reduced after phosphate deprivation but that there were no differences in serum phosphorus levels after dietary phosphate loading in 66 healthy adults. Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included those inherent in studies of observational design, dietary differences between countries, the limited reliability of the methods used for quantification of dietary phosphorus intake, and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Serum phosphorus concentration, target organs, and biomarkers. Three observational studies evaluated associations between serum phosphorus concentrations and target organs and biomarkers. Specific biomarkers that were evaluated in the studies include biomarkers of bone metabolism that were identified as serum alkaline phosphatase (ALP), bone-specific ALP (BALP), and osteocalcin; a biomarker of cardiac function that included LVM; and a biomarker of coronary artery disease that included coronary artery calcification (CAC).

Serum phosphorus concentrations and serum biochemical parameters, including serum ALP, BALP, and osteocalcin, were measured in 193 healthy, young Japanese subjects who consumed normal diets (Haraikawa and others 2012). Data from 3-d food records were analyzed using the results from blood sample collections. Details of the study are provided in Section "Total dietary phosphorus, target organs, and biomarkers". Mean (±SD) fasting serum phosphorus levels were 3.6 (±0.5) mg/dL. There was a significant negative correlation between BALP activity and serum phosphorus levels ($r = -0.165$; $P = 0.022$) as well as between BALP activity and dietary phosphate intake ($r = -0.226$; $P = 0.002$). There was also a statistically significant association between serum BALP and serum osteocalcin ($P < 0.001$) and between BALP and FGF-23 ($P = 0.008$), but not between serum BALP and serum calcium ($P = 0.524$).

The Heart and Soul observational study evaluated the association of serum phosphorus with LVM in 978 outpatients (mean age: 67 y; 81% male, 19% female) with stable CVD (Saab and others 2010). Subjects with prevalent and stable CVD were recruited from outpatient clinics. Transthoracic echocardiography was used to measure LVM at rest on the same day as serum phosphorus measurements. LVM was derived from wall thickness measurements and indexed to body surface area. For the purpose of this analysis, left ventricular hypertrophy (LVH) was determined as LVM greater than 110 g/m^2 in both men and women. The association of serum phosphorus with LVM differed by sex (interaction, $P = 0.04$). In this study, women had statistically significantly higher serum phosphorus levels than men. In models adjusted for age, race, kidney function, smoking, diabetes, blood pressure (BP), cholesterol, C-reactive protein (CRP), and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use, each 1 mg/dL higher serum phosphorus level was associated with a 4.52 g/m^2 greater LVM (95% confidence interval [CI]: 1.04 to 8.01; $P = 0.01$) in men. However, no statistically significant association was detected

Table 2–Physiological variables examined and timing of serum phosphorus concentration determination.

Study reference	Number of subjects	Timing of serum phosphate level determination	Physiological variables correlated with serum phosphorus concentrations
Antoniucci and others (2006)	13	Fasting	FGF-23, PTH
Portale and others (1996)	16	Fasting and after meals	Vitamin D, PTH
Brot and others (1999)	510	Fasting	PTH, vitamin D metabolites
Karp and others (2007)	16	Fasting	PTH
Bansal and others (2013)	810	Fasting	PTH, $25(OH)_2D$, 24, $25(OH)_2D$, BMD

$1,25(OH)_2D$, dihydroxyvitamin D; $24,25(OH)_2D$, 24,25-dihydroxycholecalciferol; 25(OH)D, 25 hydroxyvitamin D; BMD, bone mineral density; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone.

between serum phosphorus and LVM in women. The analysis of LVH revealed that each 1 mg/dL higher serum phosphorus levels in men was associated with a 39% higher odds of LVH in the multivariable model ($P = 0.04$). In contrast, higher serum phosphorus levels were associated with a 51% lower odds of LVH in women ($P = 0.03$). Of the 181 women, 45 (25%) took HRT. These women had mean serum phosphorus levels of 3.8 ± 0.6 mg/dL compared with 4.1 ± 0.7 mg/dL in non-HRT users ($P = 0.005$). However, the association of serum phosphorus with LVM differed qualitatively by HRT use and there was no association of serum phosphorus with LVM, while among nonusers there was an inverse association of serum phosphorus with LVM. Both associations were not statistically significant. The results from this study demonstrated that higher serum phosphorus levels were associated with greater LVM in men, but not in women, with stable CVD; and higher serum phosphorus levels were associated with increased odds of LVH in men and decreased odds of LVH in women. The authors stated that further study will be needed to determine whether sex hormone differences may account for the differences in association between men and women.

The Spokane Heart Study was a long-term observational study of healthy adults who were assessed every 2 y for CAC and CVD risk factors (Tuttle and Short 2009). CAC was present in 28% (245 of 883) of the subjects at baseline. After 6 y, new onset CAC developed in 33% (122 of 371) of subjects, yielding an overall prevalence of 50% (252 of 503; $P < 0.001$). In addition, a statistically significant increase in severity of CAC was observed ($P < 0.001$). The eGFR and serum phosphorus levels were not different in the presence or absence of CAC at baseline. Multivariate analyses revealed that higher serum phosphorus concentration was an independent predictor of new onset or worsening CAC as were baseline CAC scores, lower eGFR levels, and traditional CVD risk factors. Each 1-mg/dL increase in serum phosphorus imparted increased risk for CAC (incidence odds ratio [OR] = 1.61; [95% CI: 1.20 to 2.14; P = 0.001]; prevalence OR = 1.54 [95% CI: 1.17 to 2.04; $P = 0.002$]), comparable to traditional CVD risk factors. The authors concluded that the prevalence and severity of CAC increased over time and higher levels of serum phosphorus, a putative CVD risk factor, and reduced kidney function at levels conventionally considered to be within the normal range, independently predicted the occurrence of CAC in addition to traditional CVD risk factors. The results demonstrated that the prevalence and severity of CAC increased over time, and traditional CVD risk factors were associated with the increase of CAC. In addition, the authors concluded that higher serum phosphorus levels and reduced kidney function independently predicted the occurrence of CAC.

In summary, the results from 3 studies demonstrated a statistically significant association between serum phosphorus concentrations and changes in target organs or biomarkers. There was a significant negative correlation between BALP activity and serum phosphorus concentration (Haraikawa and others 2012). The results from an observational study revealed that higher serum phosphorus levels were associated with greater LVM in men but not in women, and with increased odds of LVH in men and decreased odds in women (Saab and others 2010). A long-term observational study that followed healthy individuals for 6 y for new onset CAC and CVD risk factors determined that higher serum phosphorus concentrations were an independent predictor of new onset and worsening CAC, as were other risk factors, including baseline CAC scores, lower eGFR levels, and traditional CVD risk factors (Tuttle and Short 2009). The results from this study suggested that the prevalence and severity of CAC increased over time, and that higher levels of serum phosphorus, and reduced kidney function at levels conventionally considered to be within the normal range, independently predicted the occurrence of CAC in addition to traditional CVD risk factors.

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included the limited utility of serum phosphorus concentration to serve as a marker of dietary phosphorus intake and the limited ability of the outcomes examined to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies". The quality of evidence for these 3 studies is considered low according to the grading system used in the white paper: the system is described in Appendix C.

Serum phosphorus concentration, regulatory hormones, and other physiological outcomes. The association of serum phosphorus concentrations with regulatory hormones and physiological outcomes was described in 5 primary publications included in the white paper review: 2 observational studies, 1 randomized, controlled trial, and 2 prospective, interventional studies. A summary of physiological variables examined and the timing of serum phosphate level determination is presented in Table 2. All specimens for determination of serum phosphorus levels were collected under fasting conditions.

A 4-wk, prospective, interventional study evaluated the association of serum phosphorus with changes in dietary phosphorus intake and serum concentrations of vitamin D metabolites, FGF-23, and PTH in 13 healthy male volunteers (age: 28 to 43 y) (Antoniucci and others 2006). Subjects received 3 diets with different quantities of phosphorus: (1) control = 1500 mg/d; (2) supplemented (mixture of Na_2HPO4/K_2HPO4) = 2300 mg/d; and (3) restricted = 625 mg/d. Changes in serum FGF-23 and intact PTH concentrations were associated with differences in dietary phosphorus but not with serum phosphorus concentrations. Serum phosphorus concentrations that were measured in the morning fasting state did not change with alterations in dietary phosphorus intake, nor did they correlate with serum FGF-23 concentrations ($r = 0.05$; $P = 0.7$). The study is described in

detail in Section "Association of phosphorus load with regulatory hormones and other physiological outcomes".

In total, 810 postmenopausal women from the MESA observational cohort were evaluated for associations of estrogen therapy (ET) with serum concentrations of phosphorus, calcium, FGF-23, metabolites of vitamin D (25-hydroxyvitamin D [25(OH)D], 24,25-dihydoxyvitamin D [24,25$(OH)_2$D]), and urinary fractional excretion of calcium and phosphorus (Bansal and others 2013). In an unadjusted analysis (not adjusted for age, race/ethnicity, education level, site, season, current or former tobacco use, history of cancer, physical activity level, BMI, eGFR, urine albumin-to-creatinine ratio, thiazide diuretics, and loop diuretics), mean serum phosphorus, PTH, and FGF-23 were statistically significantly lower among women who used ET, whereas 25(OH)D and 24,25$(OH)_2$D were both higher. In addition, mean fractional excretion of phosphorus (FEP) was significantly higher after multivariable adjustment in women taking ET, indicating greater urinary phosphorus excretion. However, mean PTH or FGF-23 concentrations did not differ in women who did or did not take ET after multivariable adjustment. ET was independently associated with higher 25(OH)D and 24,25$(OH)_2$D concentrations and with both lower serum calcium and fractional excretion of calcium.

There was no statistical relationship between fasting serum phosphate concentrations and serum levels of PTH or vitamin D metabolites in an observational study of 510 healthy Danish perimenopausal women (age: 45 to 58 y) (Brot and others 1999). Refer to Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes" for a description of the study design.

In a prospective, interventional study that evaluated adult healthy men, serum phosphorus concentrations were lower in elderly men (mean age: 71 y) than in younger men (mean age: 29 y); both groups received low, normal, and high intakes of phosphorus through restriction of phosphorus intake or supplementation of food with sodium and potassium phosphate solutions (Portale and others 1996). Section "Association of phosphorus load with regulatory hormones and other physiological outcomes" provides a description of the study design. The 24-h mean serum phosphorus concentrations decreased significantly when phosphorus intake was reduced from 2300 to 625 mg/d and the magnitude of the decrease was slightly greater in elderly men but this difference was statistically insignificant. Serum concentrations of 1,25$(OH)_2$D varied inversely with 24-h mean serum phosphorus concentrations ($r = -0.92$; $P < 0.0001$). At any serum phosphorus concentration, serum 1,25$(OH)_2$D in elderly men was lower than that in young men. Serum PTH concentrations were reduced with reduced serum phosphate levels. However, fasting and daytime mean serum PTH concentrations were higher in elderly men than in younger men.

A randomized, controlled study evaluated the acute effects of dietary phosphorus from 3 different food sources and a phosphate supplement, administered during 24-h sessions, on calcium and bone metabolism in 16 healthy women (age: 20 to 30 y) (Karp and other 2007). This study is also summarized in Section "Association of phosphorus load with regulatory hormones and other physiological outcomes". Daily phosphorus intake that was obtained from meat, cheese, whole grains, or a phosphate supplement ranged from 500 to 1500 mg. Serum phosphate concentrations were significantly elevated during the meat ($P = 0.0001$), cheese ($P = 0.0001$), whole-grain ($P = 0.006$), and supplement ($P = 0.0001$) sessions compared with the control session. Cheese increased the serum phosphate concentration more than the other phosphate sources ($P = 0.0001$). Compared with the other diets, cheese decreased serum PTH most ($P = 0.0001$). Phosphate supplement, by contrast, increased serum PTH concentrations compared with the control session ($P = 0.039$). There were no effects of serum phosphorus levels from the meat ($P = 0.346$) or grain diets ($P = 0.498$) on serum PTH levels. The results appeared to indicate that high serum phosphorus levels associated with the phosphate supplement increased serum PTH concentrations, whereas high serum phosphate concentrations from meat and whole grains did not affect serum PTH levels and high serum levels associated with cheese products decreased serum PTH levels.

In summary, 3 studies were unable to find an association between serum phosphorus from different dietary sources with serum PTH concentrations in different populations of healthy subjects. A 4-wk study demonstrated that changes in serum FGF-23 and intact PTH concentrations were associated with differences in dietary phosphorus but not with fasting, morning serum phosphorus concentrations in healthy male volunteers (Antoniucci and others 2006). A cross-sectional study of 510 healthy Danish perimenopausal women demonstrated that there was no statistical relationship between fasting serum phosphate concentrations and PTH or vitamin D metabolites' serum concentrations (Brot and others 1999). Finally, a study that evaluated 810 postmenopausal women determined that after multivariate adjustment, ET was associated with lower mean serum phosphorus concentrations and increased FEP, but mean serum PTH or FGF-23 concentrations did not differ in women who did or did not use ET (Bansal and others 2013).

However, 2 studies demonstrated statistically significant associations of changes in serum phosphorus levels with serum PTH concentrations. An interventional study in adult healthy men showed that fasting and daytime mean serum PTH concentrations were higher in elderly men than younger men, and there was a direct correlation of serum PTH concentrations with serum phosphorus levels in both older and younger men (Portale and others 1996). In addition, serum 1,25$(OH)_2$D concentrations varied inversely with 24-h mean serum phosphorus concentrations. A randomized, controlled study evaluated the acute effects of dietary phosphorus from 3 different food sources (meat, cheese, and whole grains) and a phosphate supplement in healthy women (Karp and others 2007). Serum phosphorus concentrations increased more with cheese and a phosphate supplement than after consumption of other phosphate sources. However, serum PTH levels were reduced more with cheese than with other phosphate sources. In summary, the high serum phosphorus levels after phosphate supplementation were associated with increased serum PTH concentrations, whereas high serum phosphate concentrations from meat and whole grains did not affect serum PTH levels, and the high serum levels associated with cheese products were associated with decreased serum PTH levels.

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included the limited utility of serum phosphorus concentration to serve as a marker of dietary phosphorus intake and the limited ability of the outcomes examined to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies". The quality of evidence for these studies is considered low for 2 studies (Brot and others 1999; Bansal and others 2013), high for one study (Karp and others 2007), and

moderate for 2 studies (Portale and others 1996; Antoniucci and others 2006).

Serum phosphorus concentration and clinical outcomes. The relationships between serum phosphorus concentrations and clinical outcomes were evaluated in 14 studies. In most studies, the associations of serum phosphorus with clinical outcomes did not account for the mechanisms for changes in serum phosphorus levels, whether by dietary phosphorus or dietary supplements. These studies primarily evaluated correlations between clinical outcomes and changes in serum phosphorus levels. Table 3 summarizes the clinical outcomes variables that were evaluated in the studies. Most serum phosphorus samples were collected under fasting conditions but the conditions were not specified in 4 studies and plasma phosphorus concentrations were collected in one study. Summaries of each study are presented in this section, and the results are summarized in Appendix D, Master Clinical Table (Table D1).

The associations of serum phosphorus concentrations with cardiovascular outcomes were evaluated in 9 studies. Four of these studies also analyzed the association of serum phosphorus concentrations with deaths.

The association of fasting serum phosphorus concentrations with all-cause cardiovascular mortality was evaluated in 12984 participants aged 20 y or older who participated in the NHANES III (1988 to 1994) (Chang and Grams 2014). Participants examined in the morning sessions were instructed to fast for at least 12 h, whereas participants in the afternoon/evening sessions were instructed to fast for at least 6 h. Of the 12984 participants in the study sample, 6633 fasted at least 12 h, and 6351 fasted less than 12 h. During a median of 14.3 y of follow-up, a total of 1453 deaths occurred in those who fasted ≥12 h, and 1540 deaths occurred in those who fasted less than 12 h. Individuals who fasted at least 12 h were younger, less likely to have diabetes, less likely to have eGFR less than 60 mL/min/1.73 m^2, and had lower serum phosphorus levels, both in the morning session (3.32 compared with 3.42 mg/dL; $P = 0.01$) and afternoon/evening sessions (3.42 compared with 3.57 mg/dL; $P < 0.001$). Individuals fasting at least 12 h had lower serum phosphorus levels than those fasting less than 12 h (3.34 compared with 3.55 mg/dL; $P < 0.001$) and higher correlation with repeated measurement (0.66 compared with 0.53; $P = 0.002$).

Higher serum phosphorus concentrations were associated with both all-cause and cardiovascular mortality in adjusted analyses. For serum phosphorus levels greater than 3.5 mg/dL, every 1-mg/dL increase was associated with a 35% increased risk of all-cause death (adjusted hazard ratio [aHR]: 1.35; 95% CI: 1.05 to 1.74; $P = 0.02$). For serum phosphorus levels less than 3.5 mg/dL, every 1-mg/dL increase was associated with a 19% increased risk of death (aHR: 1.19; 95% CI: 1.00 to 1.41; $P = 0.05$). Similarly, for serum phosphorus levels above 3.5 mg/dL, every 1-mg/dL increase was associated with a 45% increased risk of cardiovascular death (aHR: 1.45; 95% CI: 1.05 to 2.00; $P = 0.03$); for serum phosphorus levels below 3.5 mg/dL, every 1-mg/dL increase was associated with a 38% increased risk of cardiovascular death (aHR, 1.38; 95% CI: 1.07 to 1.78; $P = 0.02$). When analyzed by fasting duration, the association of higher serum phosphorus levels in the interval above 3.5 mg/dL with mortality was significantly stronger for those fasting longer (≥12 compared with <12 h; P for interaction $= 0.04$). Among those fasting at least 12 h, every 1-mg/dL increase of serum phosphorus above 3.5 mg/dL was associated with an 84% increased risk of death (aHR: 1.84; 95% CI: 1.04 to 3.24; $P = 0.04$); among those fasting less than 12 h, there was no association between serum phosphorus levels above 3.5 mg/dL and all-cause mortality. Serum phosphorus below 3.5 mg/dL was not associated with all-cause mortality in either subgroup. A similar pattern was observed with cardiovascular mortality: higher serum phosphorus levels above 3.5 mg/dL conferred higher risk in those fasting longer, although this was not statistically significant. Based on the results that serum phosphorus levels varied considerably during the day, the authors concluded that the fasting duration modified the association between serum phosphorus concentrations and mortality and serum phosphorus levels were associated with all-cause and cardiovascular mortality only among those fasting for longer durations.

A nested, case–control study examined the associations between plasma phosphorus, FGF-23, and PTH concentrations and the risk of coronary heart disease (CHD) in 422 healthy men who participated in the Health Professionals Follow-up Study, had no baseline CVD or CKD, and who developed nonfatal myocardial infarction (MI) or fatal CHD after 10 y of follow-up (Taylor and others 2011). The results were compared with control subjects who were randomly selected from study participants who were alive and who did not have a history of CVD at baseline. At baseline, there were no statistically significant differences between case and control subjects in plasma levels of FGF-23, PTH, or phosphorus. Controls were selected in a 2:1 ratio and matched for age, date of blood collection, and smoking status. An analysis was performed to determine the OR for incident CHD associated with plasma FGF-23, plasma PTH, and plasma phosphorus after adjusting for matching factors, family history of MI, BMI, alcohol consumption, physical activity, history of diabetes mellitus (DM) and hypertension, ethnicity, region, plasma 25-hydroxyvitamin D, and other factors. The results accounted for a comparison of the highest to lowest quartiles for each variable (plasma FGF-23, phosphorus, PTH levels). The OR for CHD was 1.03 (95% CI: 0.70 to 1.52; P for trend $= 0.84$) for plasma FGF-23, 1.20 (95% CI: 0.82 to 1.76; P trend $= 0.99$) for plasma PTH, and 0.72 (95% CI: 0.51 to 1.02; P trend $= 0.13$) for plasma phosphorus. The authors concluded that they observed no associations between plasma levels of FGF-23, intact PTH, and phosphorus and subsequent risk for incident nonfatal MI or fatal CHD.

A large, prospective, community-based cohort study of middle-aged, healthy men, who participated in the Uppsala Longitudinal Study of Adult Men, evaluated the relationship of serum calcium and phosphorus levels to total, cardiovascular, and non-cardiovascular mortality (Larsson and others 2010). There were 2 prespecified subgroup analyses: (1) individuals with eGFR >90 mL/min/1.73 m^2; and (2) individuals with normal or low serum calcium and phosphorus levels. Between 1970 and 1973, all men born between 1920 and 1924 and residents in the municipality of Uppsala, Sweden, were invited to participate in the health survey. Of the 2322 men enrolled, this analysis included a subsample of 1777 men with eGFR >90 mL/min/1.73 m^2, and another subsample of 2155 men with serum calcium <2.6 mmol/L and serum phosphorus <1.45 mmol/L (defined as the normal upper limits for healthy individuals). All blood samples were obtained in the morning after an overnight fast. Median follow-up time was 29.8 y (range: 0.04 to 32.2), yielding a total of 56534 person-years at risk. During follow-up, 1009 men died; 466 died of CVD and 543 died of noncardiovascular causes. The incidence rate of total mortality was 17.8/1000 person-years at risk (95% CI: 16.8 to 19.0), of cardiovascular mortality was 8.2/1000 (95% CI: 7.5 to 9.0), and of noncardiovascular mortality was 9.6/1000 (95% CI: 8.8 to 10.4). Two models were used to analyze relationships of serum phosphate levels and outcome; Model A adjusted

Table 3–Measurement of serum phosphorus concentrations and description of clinical outcome variables

Study reference	Number subjects	Meal status and serum phosphorus	Clinical outcome variables correlated with serum phosphorus levels
Risk of cardiovascular outcomes			
Chang and others (2014)	9686	Fasting and nonfasting	Cardiovascular and all-cause death
Taylor and others (2011)	422	NS: plasma samples	Nonfatal MI or fatal CHD
Larrson and others (2010)	2176	Fasting samples	Cardiovascular and noncardiovascular death
Dhingra and others (2010)	3300	Fasting samples	Heart failure
Foley and others (2009)	3015	Fasting samples	Coronary artery calcium
Ix and others (2009)	1370	Fasting samples	Ankle brachial index
Onufrak and others (2009)	13998	Fasting samples	Death and coronary artery disease
Dhingra and others (2007)	3368	NS	Risk of cardiovascular disease
Tonelli and others (2005)	4127	Fasting samples	Heart failure, MI, death
Risk of death			
Heimburger and others (2010)	142	NS	Risk of death
Risk of cancer			
Wulaningsih and others (2013)	397292	Fasting samples in approximately 60% subjects who had cancer	Risk of cancer
Risk of metabolic outcomes			
Lorenzo and others (2014)	863	NS	Type 2 diabetes
Hartman and others (2013)	77	Saliva levels	Obesity in children
O'Seaghdha and others (2011)	15641	Fasting samples	Incident CKD and ESRD

CHD, coronary heart disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; MI, myocardial infarction; NS, not specified; P, phosphorus; PTH, parathyroid hormone.

for serum albumin, eGFR, and age, and Model B, incorporating relevant cardiovascular risk factors, adjusted for albumin, eGFR, diabetes, use of antihypertensive medication, systolic and diastolic BP, total cholesterol, triglycerides, age, BMI, and smoking. In both models, a 1-SD-higher serum phosphorus concentration was associated with a 6% to 7% higher risk of total mortality and a 7% to 10% higher risk for cardiovascular mortality. A 1-SD-higher serum phosphorus concentration was also associated with a 7% higher risk of noncardiovascular mortality in Model A but was associated with a 2% statistically nonsignificant higher risk in Model B. In subjects with eGFR >90 mL/min/1.73 m^2, the relationships of serum phosphorus to total mortality and to cardiovascular mortality were nearly identical. A similar analysis demonstrated that increased serum calcium was associated with an increased risk of cardiovascular, noncardiovascular, and total mortality. The analysis revealed that there was no additive effect of serum calcium and phosphorus levels on total mortality. Modeling of the calcium–phosphorus product ([CP-P]) revealed a 1-SD-higher product was associated with a 7% to 8% higher risk in total mortality and 8% to 10% greater risk of cardiovascular mortality. The authors concluded that this long-term, longitudinal study extending over nearly 30 y provides evidence that higher serum calcium concentration, higher serum phosphorus concentration, and higher CP-P were each associated with higher total mortality risk in middle-aged men. A higher serum calcium concentration was mainly associated with noncardiovascular mortality, and a higher serum phosphorus concentration and CP-P were associated with cardiovascular mortality. Higher serum phosphorus concentration was also associated with higher total mortality.

A study evaluated the relationship of serum phosphorus concentrations to echocardiographic left ventricular measurements cross-sectionally and to the incidence of heart failure prospectively in 3300 healthy adults (mean age: 44 y, 51% women) free of heart failure, MI, and CKD (Dhingra and others 2010). Each mg/dL increment in serum phosphorus concentration was associated with a 1.74-fold risk of heart failure [95% CI: 1.17 to 2.59]. Individuals in the highest serum phosphorus quartile experienced a 2-fold (95% CI: 1.28 to 3.40) increased risk of heart failure compared with participants in the lowest quartile. These relations were maintained upon additional adjustments for baseline LVM/dimensions and systolic dysfunction. In analyses restricted to individuals with eGFR >90 mL/min/1.73 m^2, no proteinuria and serum phosphorus levels <4.5 mg/dL, the association of serum phosphorus with heart failure remained robust.

The association between serum phosphorus levels and coronary artery atherosclerosis was evaluated in 3015 healthy young adults from a community-based cohort of the prospective Coronary Artery Risk Development in Young Adults (CARDIA) study (Foley and others 2009). The study measured CAC, which is considered a reflection of the degree of atherosclerosis. Serum phosphorus levels were measured at baseline, and CAC was assessed by evaluating computed tomography 15 y later. At baseline, mean age was 25.2 y, 54.4% were women, 45.0% were black, and the mean serum phosphorus concentration was 3.6 mg/dL. Most subjects had no kidney disease, and the mean eGFR was 116.6 mL/min/1.73 m^2, and only 0.2% had glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. After 15 y, 3.2% of the study population had minimal CAC, 4.8% had mild calcification, 1.1% had moderate calcification, and 0.5% had severe calcification. In multivariate models, higher phosphorus levels were associated with greater likelihood of higher CAC score categories (adjusted OR = 1.17 per 0.5 mg/dL; $P = 0.0331$). The multivariate analysis suggested that phosphorus levels >3.9 mg/dL were associated with greater likelihood of coronary artery calcium score ≥100, while serum calcium and CP-P levels had no association with CAC. Higher serum phosphorus levels, even within the normal range, were associated with high coronary artery calcium and, the authors concluded, may represent a risk factor for coronary artery atherosclerosis in healthy young adults.

A study evaluated the association of serum calcium, phosphate, and calcium-phosphate product levels with cardiovascular events including with CHD, stroke, and death in community dwelling adults (Foley and others 2008). A total of 15732 community-based subjects were evaluated over a period of 12.6 y in the Atherosclerosis Risk in Communities (ARIC) Study. Mean age of the study population was 54.2 y; 55.2% were women and 27.1% were African American. Mean serum phosphate was 3.4 mg/dL; calcium, 9.8 mg/dL; calcium-phosphate product, 33.6 mg2/dL2;

and GFR, 93.1 mL/min/1.73 m^2. Shared multivariate associations of calcium, phosphate, and calcium-phosphate product included older age, female sex, African American race, cigarette-years, current cigarette smoking, low BMI, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, low serum albumin, low GFR, low caloric intake, and phosphorus intake. For phosphate, low levels were associated with CHD (HR, 0.90) and high levels with death (HR, 1.12). For calcium-phosphate product, low levels were associated with CHD (HR, 0.92), and high levels with stroke (HR, 1.10) and death (HR, 1.13). Serum phosphate levels were associated with stroke (aHR 1.11; $P = 0.0291$) and death (aHR 1.14; $P < 0.0001$) but was not associated with CHD (aHR = 1.03). Calcium-phosphate product was associated with both stroke (aHR 1.15; $P < 0.0017$) and death (aHR 1.15; $P < 0.0001$) but was not associated with CHD (aHR, 1.03). Findings within subgroups were similar to those seen in the overall population, except for the lack of association between phosphate levels and stroke for participants with CVD at baseline. This study demonstrated an association between the serum calcium-phosphate product and serum phosphorus with clinical outcomes of stroke and death in a community-based population.

The association of serum phosphorus concentration with arterial stiffness was evaluated by measuring ankle brachial index (ABI), pulse pressure, and large and small artery elasticity by radial artery waveform analysis in 1370 individuals with a mean age of 64 ± 10 y, 55% female, who did not have clinical CVD, and participated in the MESA observational study (Ix and others 2009). Dietary intake of total calories, fat, calcium, and phosphorus did not differ significantly across phosphorus groups. The mean serum phosphorus concentration was 3.5 ± 0.5 mg/dL, and mean eGFR was 71 ± 19 mL/min/1.73 m^2 (440 [32%] had eGFR <60 mL/min/1.73 m^2). Higher serum phosphorus concentrations were associated with higher LDL, HDL, triglyceride, and CRP levels and lower eGFR. Individuals with phosphorus concentrations greater than 4 mg/dL had approximately twice the prevalence of high ABI compared with participants with phosphorus concentrations less than 4 mg/dL. Subjects with serum phosphorus concentrations greater than 4 mg/dL were at significantly increased risk for high ABI compared with those with serum phosphorus less than 3 mg/dL ($P = 0.05$), whereas participants with intermediate phosphorus concentrations had a risk similar to individuals with serum phosphorus less than 3 mg/dL. In a fully adjusted model, higher serum phosphorus concentrations were associated with higher pulse pressure and lower large and small artery elasticity but there was no statistically significant difference in models adjusted for age, sex, and race/ethnicity. In conclusion, there was a strong and independent association of higher serum phosphorus concentrations with high ABI among individuals without clinically recognized CVD.

A prospective cohort was examined for sex heterogeneity in the association of serum phosphorus concentration with all-cause mortality and incident coronary artery disease using data from the ARIC study (1987 to 2001) (Onufrak and others 2009). The ARIC enrolled 15732 healthy subjects aged 45 to 64 y from the general population. The analysis evaluated data from 13998 subjects (56.6% women, 24.7% blacks) with no diabetes or CVD and with GFR >60 mL/min/1.73 m^2. Fasting serum phosphorus levels were obtained at baseline. The result indicated that serum phosphate levels were mostly within the normal range (2.5 to 4.5 mg/dL). The mean serum phosphorus level was significantly higher among women (3.56 mg/dL; SD: 0.46) than among men (3.25 mg/dL; SD: 0.45; $P < 0.0001$). Current use of estrogen replacement therapy and hypertension were associated with lower serum phosphorus levels, while postmenopausal status and current smoking were associated with higher serum phosphorus levels. Total cholesterol, HDL cholesterol, and triglycerides were positively associated with serum phosphorus levels, while BMI was negatively associated. Age, black race, diabetes, eGFR, and fibrinogen were not significantly associated with serum phosphorus levels. The age-adjusted rates of coronary artery disease in men were 35% greater with serum phosphorus levels <3.1 mg/dL, 43% greater with serum phosphorus levels 3.6 to 3.8 mg/dL, and 81% higher with serum phosphorus levels >3.8 mg/dL than in men with serum levels of 3.1 to 3.3 mg/dL. Elevated phosphorus serum levels were not associated with increased coronary artery disease in this model. In a multivariable-adjusted model, men in the highest quintile of serum phosphorus level (>3.8 mg/dL) had an increased mortality rate (HR = 1.45, 95% CI: 1.12 to 1.88), while women did not (HR = 1.18; 95% CI: 0.89 to 1.57). When serum phosphorus levels were greater than 3.8 mg/dL, the age-adjusted mortality rate was elevated to 73% (95% CI: 34 to 224) among men and 35% (95% CI: 2 to 79) among women. There was no significant association of serum phosphorus concentrations with coronary artery disease and sex ($P = 0.195$). The results suggested that there was sex heterogeneity in the association of serum phosphorus levels with mortality among members of the general population who are free of CVD and overt renal failure, with higher phosphorus levels being associated with increased mortality among men but not among women.

Data were analyzed from the Framingham Offspring Study that evaluated participants who had levels of serum phosphorus and calcium measured routinely at the 2nd examination cycle (1979 to 1982) ($n = 3368$) (Dhingra and others 2007). Patients excluded from the analysis had prevalent CVD ($n = 167$), defined as any history of CHD, cerebrovascular disease, peripheral vascular disease, or heart failure, and an eGFR of <60 mL/min/1.73 m^2 at baseline. After exclusions, a total of 3368 individuals (51% of whom were women) were evaluated. Subjects had a physical examination at each visit. Incident CVD was defined as fatal or nonfatal MI, angina pectoris (stable or unstable), cerebrovascular events (stroke or transient ischemic attacks), peripheral vascular disease, or congestive heart failure. The prevalence of several established CVD risk factors (other than smoking) decreased with increasing levels of phosphorus. In a multivariable linear regression model, serum phosphorus concentrations were positively associated with age, high-sensitivity CRP, eGFR, serum albumin level, and total HDL cholesterol ratio but were inversely related to BMI, systolic BP, and hemoglobin level ($P < 0.02$ for all). Multivariable-adjusted levels of serum phosphorus were lower in men compared with women ($P < 0.001$). Serum phosphorus levels were weakly and positively correlated with serum calcium levels ($r = 0.12$ in men and 0.16 in women; $P < 0.001$ for both). Subsequently, during a mean follow-up period of 16.1 y, 524 participants experienced a 1st CVD event (159 in women). The events included 138 MIs, 173 angina pectoris events, 93 cerebrovascular events, 18 sudden cardiac deaths, 63 peripheral vascular disease, and 39 congestive heart failure events. The results indicated a statistically significant linear trend for increasing risk of CVD across quartiles of serum phosphorus concentrations. The age- and sex-adjusted incidence of CVD rose across quartiles of serum phosphorus levels (range across quartiles: 16.4% compared with 21.1%). After adjusting for age and sex, the HR for incident CVD relative to a 1-mg/dL increase in serum phosphorus levels was 1.17 (95% CI: 0.96 to

1.44; $P = 0.12$). After adjusting for all other covariates, there was a statistically significant increase in the risk of CVD with increasing serum phosphorus levels (HR for a 1-mg/dL [0.3229 mmol/L] increase of 1.31; 95% CI: 1.05 to 1.63; $P = 0.02$). The CP-P was also positively related to CVD risk (HR = 1.12 increase per SD increment; 95% CI: 1.02 to 1.24; $P = 0.02$). In summary, there was a statistically significant association of serum phosphorus concentrations (and the highly correlated CP-P) with an increased risk of incident CVD in a continuous fashion in multivariable models adjusting for high-sensitivity CRP, across all quartiles, and in a model incorporating established CVD risk factors as time-varying covariates. Serum phosphorus levels greater than 3.5 mg/dL were associated with a 55% increased CVD risk. While the CP-P was correlated with increased CVD risk, the results revealed that serum calcium levels were not related to incident CVD in any of the models.

A *post hoc* analysis of data from a randomized clinical trial (Cholesterol And Recurrent Events trial) evaluated the association of serum phosphate levels with cardiovascular events in subjects with CHD (Tonelli and others 2005). Baseline serum phosphate levels were evaluated in 4127 fasting participants who were randomized to receive pravastatin 40 mg daily or placebo and followed up for a median of 59.7 mo. During the follow-up period, 375 subjects died. Baseline serum phosphate levels were significantly associated with the age-, race-, and sex-adjusted risk of all-cause death (HR per 1 mg/dL = 1.27; 95% CI: 1.02 to 1.58; $P = 0.03$). After dividing subjects into 4 categories based on baseline serum phosphorus levels (<2.5, 2.5 to 3.4, 3.5 to 3.9, and ≥4 mg/dL), a graded relation between phosphate and death was observed after adjustment for age, race, and sex (P for trend = 0.03). After adjusting for risk factors, higher serum phosphorus levels were associated with increased risk of new heart failure (P for trend = 0.02), MI (P for trend = 0.04), and the composite of coronary death or nonfatal MI (P for trend = 0.04), but not the risk of stroke (P for trend = 0.33). Individuals with serum phosphorus concentrations ≥4 mg/dL had a fully adjusted HR for experiencing the composite outcome of coronary death or nonfatal MI of 1.32 (95% CI: 0.95 to 1.84) and a fully adjusted HR for experiencing an MI of 1.50 (95% CI: 1.05 to 2.16) compared with those with serum phosphate of 2.5 to 3.4 mg/dL. Several characteristics were statistically significantly associated with higher serum phosphorus levels, including female sex, black race, diabetic status, higher levels of serum albumin, lower levels of hemoglobin, and current smoking. Serum phosphorus was inversely correlated with kidney function when baseline GFR was <60 mL/min/1.73 m^2 and was directly correlated with kidney function when baseline GFR was ≥60 mL/min/1.73 m^2. Most participants in the study had normal or nearly normal kidney function. Use of β-adrenergic blockers and higher levels of alcohol consumption were also associated with higher serum phosphate levels, although the magnitude of the increase was small. The authors concluded that a graded, independent relationship was found between higher levels of serum phosphate and the risk of death and cardiovascular events in people with prior MI, most of whom had serum phosphate levels within the normal range.

Risk of death in human immunodeficiency virus (HIV)-infected individuals. An observational cohort of 142 HIV-infected adults in Lusaka, Zambia, with BMI <16 kg/m^2 or CD4+ T cell lymphocyte count <50 cells/μL or both, who had advanced immunosuppression and severe malnutrition, and who were initiating antiretroviral therapy (ART) were followed prospectively during the 1st 12 wk of ART (Heimburger and others 2010). The authors observed that metabolic abnormalities are transiently exacerbated by the introduction of ART in patients with advanced HIV disease and malnutrition in developing countries. This study was conducted to assess the association of serum phosphorus levels with mortality in HIV-infected individuals who had severe malnutrition and/or advanced immunosuppression and initiating ART, to further understand the excess mortality observed in these patients. A serum metabolic panel, including serum phosphate levels and high-sensitivity CRP, was monitored. The primary outcome measure was mortality during the 1st 12 wk of ART. ART consisted of recommended first-line therapy of a nonnucleoside reverse transcriptase inhibitor combined with 2 nucleoside reverse transcriptase inhibitors. When deficiencies of phosphate were detected, interventions, including increasing dietary phosphate or phosphate supplements, were administered according to a predetermined algorithm based on phosphate serum levels. In total, 44 (31%) participants had serum phosphorus levels <0.87 mmol/L at some point during the study, and received at least dietary counseling. Baseline serum phosphorus concentration was significantly higher among participants alive at 12 wk (median: 1.30 mmol/L; interquartile range: 1.04, 1.43), than in those who had died (median: 1.06 mmol/L; interquartile range: 0.89, 1.27; $P \leq 0.01$). Other measured electrolytes were not significantly associated with mortality. After adjusting for sex and age, and baseline CD4+ T lymphocyte count, BMI, and hemoglobin, low baseline serum phosphorus concentration was associated with an increased risk of death within 12 wk of ART initiation ($P = 0.008$). Each 0.1 mmol/L increase in baseline phosphate was associated with an incremental decrease in mortality (aHR: 0.83; 95% CI: 0.72 to 0.95). The association was independent of other metabolic parameters and known risk factors for early ART-associated mortality in sub-Saharan Africa. While participant attrition presented a limitation, it was consistent with local program experience. The authors concluded that low serum phosphorus concentration at ART initiation was an independent predictor of early mortality among HIV patients with severe malnutrition or advanced immunosuppression.

Risk of cancer. Data from the Swedish Apolipoprotein Mortality Risk Study (AMORIS) database that collected data from 1985 to 1996 were analyzed to evaluate the association of serum phosphorus concentrations with the overall incidence of cancer (Wulaningshi and others 2013). The study included 397292 individuals without cancer at baseline (age: 20 y of age or older), with baseline measurements of serum phosphorus, calcium, and other laboratory measures. During a mean follow-up of 12.75 y, 31482 individuals (mean age: 55.71 ± 11.93 y) developed cancer and 365810 individuals (mean age: 44.0 ± 14 y) did not. Fasting blood samples were collected from 62% of individuals who had cancer and from 57% of individuals who did not have cancer. Multivariate Cox proportional hazards models were used to investigate quartiles and standardized values of serum phosphorus as a continuous variable in relation to overall incident cancer. The age of individuals and serum glucose, ALP, and creatinine levels were higher in the population with cancer; serum phosphorus levels were slightly higher in the group without cancer; and there were no marked differences in calcium levels between the 2 groups. The concentrations of serum phosphorus in the quartiles were <0.95, 0.95 to 1.05, 1.05 to 1.16, and ≥1.16. The risk of cancer was analyzed according to quartiles and according to standardized serum concentrations of phosphorus. There was a statistically significantly lower risk of overall cancer in individuals in the 3rd and 4th quartiles of serum phosphorus (P for trend <0.0001) for men and women combined.

Analysis of the standardized concentrations of serum phosphorus revealed that there was a greater overall cancer risk with increasing serum phosphorus levels in men (HR: 1.02 [95% CI: 1.00 to 1.04] for every SD increase in serum phosphorus) and that there was a negative association in women (HR: 0.97 [95% CI: 0.96 to 0.99] for every SD increase in serum phosphorus). Further analyses of specific cancer sites revealed a positive association between serum phosphorus quartiles and the risks of cancer of the pancreas, lung, thyroid gland, and bone in men, and cancer of the esophagus, lung, and nonmelanoma skin cancer in women. Conversely, the risks for developing breast and endometrial cancer as well as other endocrine cancer in both men and women were lower in those with higher serum phosphorus levels. The authors concluded that the inverse association between serum phosphorus levels and risk of breast, endometrial, and other endocrine cancers may indicate the role of hormonal factors in the relation between phosphorus metabolism and cancer.

Metabolic outcomes: CKD and Type 2 diabetes (T2D). A study examined the relationships of calcium and phosphate levels and the calcium–phosphate product with the development of T2D in 863 African Americans, Hispanics, and non-Hispanic whites who participated in the Insulin Resistance Atherosclerosis Study (IRAS) and who were free of diabetes at baseline (56% women; age range: 40 to 69 y) (Lorenzo and others 2014). Mean follow-up period was 5.2 y. T2D was assessed during a 1st baseline visit and follow-up visits, where a 75-g oral glucose tolerance test was administered. During a 2nd baseline visit, insulin sensitivity and insulin secretion were determined using the frequently sampled intravenous glucose tolerance test. Diabetes was defined as fasting glucose ≥7.0 mmol/L and/or 2-h glucose ≥11.1 mmol/L, and impaired glucose tolerance as 2-h glucose ≥7.8 to 11.0 mmol/L. Individuals who reported current treatment with glucose-lowering medications were considered to have diabetes. Mean (range) calcium and phosphate concentrations were 2.25 (1.52 to 3.02) and 1.02 (0.13 to 1.55) mmol/L, respectively. The demographically adjusted risk of developing diabetes was 72% higher in individuals with serum phosphorus concentrations ≥1.20 mmol/L than in those with phosphorus concentration <1.20 mmol/L (OR: 1.72 [95% CI: 1.03 to 2.87]). Calcium concentrations (OR per 1-SD unit increase, 1.26 [95% CI: 1.04 to 1.53]) and the calcium–phosphate product (OR: 1.29 [95% CI: 1.04 to 1.59]) were also associated with incident diabetes after adjustment for demographic variables, family history of diabetes, and 2-h glucose. After adjusting for demographic variables, the association between serum phosphorus concentrations and progression to diabetes was not statistically significant (OR: 1.21 [95% CI: 0.98 to 1.49]). Calcium concentration (OR: 1.37 [95% CI: 1.09 to 1.72]) and calcium–phosphate product (OR: 1.39 [95% CI: 1.09 to 1.77]) remained associated with incident diabetes after additional adjustment for BMI, plasma glucose, insulin sensitivity index, acute insulin response, CRP, eGFR, diuretic drugs, and total calcium intake. There was no effect of sex, race/ethnicity, family history of diabetes, and glucose tolerance on the relationship between calcium concentration, phosphate concentration, or calcium–phosphate product and incident diabetes ($P > 0.37$), indicating consistent relationships across categories of these variables. The authors concluded that serum calcium concentration and calcium–phosphate product were associated with the development of T2D. The results demonstrated no association between serum phosphorus concentrations alone and the development of T2D. These associations were independent of the effect of adiposity, glucose tolerance, insulin sensitivity, insulin secretion, and subclinical inflammation.

Risk of incident CKD or end-stage renal disease (ESRD). Two population-based prospective cohort studies examined whether serum phosphorus levels were associated with an increased risk of incident CKD or ESRD (O'Seaghdha and others 2011). The studies evaluated data from 2269 participants free of CKD (had baseline eGFR <60 mL/min/1.73 m^2) from the Framingham Heart Study (FHS) (mean age: 42 y; 53% women) and 13372 participants from the NHANES III (mean age: 44.3 y, 52% women). In the FHS, the relationship between baseline phosphorus category (<2.5 mg/dL, 2.5 to 3.49 mg/dL, 3.5 to 3.99 mg/dL, and ≥4 mg/dL) and incident CKD ($n = 267$) was examined. The relationship between serum phosphorus concentrations below and above 4 mg/dL in relation to incident ESRD ($n = 65$) was analyzed in the NHANES III. Fasting serum phosphorus levels were drawn at the baseline visit in the FHS. In the NHANES III, a random subset of approximately one-third of participants had overnight fasting phosphate levels while nonfasting levels were obtained in the remaining subjects. FHS participants with the highest phosphorus serum levels (≥4 mg/dL) had an increased risk of CKD [OR: 2.14; 95% CI: 1.07 to 4.28; $P = 0.03$] in multivariable-adjusted model adjusted for CKD risk factors when compared with the reference group (2.5 to 3.49 mg/dL). Similarly, in the NHANES III, participants with phosphorus levels ≥4 mg/dL, compared with those with phosphorus levels <4 mg/dL, had an increased risk of incident ESRD (RR: 1.90; 95% CI: 1.03 to 3.53; $P = 0.04$). The results indicated that serum phosphorus levels in the high-normal range were associated with a doubling of the risk of developing new onset CKD and ESRD.

One study analyzed the phosphate content in saliva collected from children ($n = 77$; mean age: 10.5 ± 1.8) to evaluate association with BMI (Hartman and others 2013). Paired 100-μl samples of saliva and plasma were collected from each child and phosphate concentrations were measured using gas chromatography/mass spectrometry. The results revealed that different obesity parameters, including BMI, waist circumference, fitness, and weight, along with a cardiovascular parameter (systolic BP), were significantly associated with salivary phosphate content. There was a significantly higher salivary phosphate content in obese children than in normal-weight children (analysis of variance [ANOVA], $P < 0.001$). The correlation coefficient (r) between BMI and salivary phosphate concentration was 0.33 ($P = 0.0032$). However, there was no association of obesity with plasma phosphate concentrations ($P = 0.58$). The authors suggested that the human salivary phosphate level may be an early predictive biomarker of the development of obesity in children. It should be noted that this study did not measure the development of obesity or the changes in plasma or salivary phosphorus concentrations in each child over time. This study evaluated the association of obesity with plasma and salivary phosphorus concentrations at a distinct time point for each child.

The results from the previous 13 studies that evaluated the association of serum phosphate concentrations with clinical outcomes are as follows:

- The results from 9 studies demonstrated that higher serum phosphorus levels were associated with increased risk of incident CVD and in 5 of the studies, higher serum phosphorus concentrations were associated with an increased risk of cardiac mortality. Increased serum phosphorus levels were associated with incident heart failure in healthy individuals (Foley and others 2008; Dhingra and others 2010; Larsson and others 2010), and with increased risk of death and

cardiovascular events in people with CVD or prior MI (Tonelli and others 2005; Dhingra and others 2007). Higher serum phosphorus levels were associated with high coronary artery calcium, which in healthy young adults, may represent a risk factor for coronary artery atherosclerosis (Foley and others 2008). Higher serum phosphorus concentrations, within the normal range, were associated with higher pulse pressure and lower large and small artery elasticity in individuals without CVD (Ix and others 2009).

- In HIV-infected patients with advanced immunosuppression and severe malnutrition in Zambia, low baseline serum phosphorus concentrations were associated with an increased risk of death within 12 wk of initiating ART (Heimburger and others 2010).
- A greater overall cancer risk was associated with increasing serum phosphorus levels in men while a negative association of cancer was associated with increasing serum phosphorus levels in women in an analysis of data from a large prospective cohort that included 31482 individuals (Wulaningsih and others 2013). An inverse association between serum phosphorus levels and risk of breast, endometrial, and other endocrine cancers may indicate the role of hormonal factors in the relation between phosphorus metabolism and cancer.
- High serum phosphorus concentrations were associated with progression to T2D (Lorenzo and others 2014).
- High serum phosphorus concentrations that were within the normal range were associated with an increased risk of developing CKD and ESRD (O'Seaghdha and others 2011).
- In children, higher phosphate concentrations measured in saliva (but not in serum) were associated with obesity (Hartman and others 2013).

All studies discussed in Section "Serum phosphorus concentration and clinical outcomes" and its subsections were observational studies. Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included those inherent in studies of observational design and the limited utility of serum phosphorus concentration as a marker of dietary phosphorus intake. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies". The quality of evidence for all studies that evaluated the association of serum phosphorus concentrations with clinical outcomes is considered low according to the grading system used in the white paper: the system is described in Appendix C.

Dietary phosphorus, target organs, and biomarkers

The white paper review includes 16 primary research publications that evaluated the association between dietary phosphorus and target organ effects or biomarkers; 3 of these studies evaluated associations with food-additive phosphates. The number of subjects evaluated in the studies ranged from as few as 11 (Shuto and others 2009) to 23652 (Kwak and others 2014). In aggregate, the studies included both male and female subjects from the United States, Finland, North Korea, and Australia; study populations were demographically diverse, with postmenopausal women, college students, and adolescents represented. Details of the search strategy, criteria for including the selected publications, and the quality rating system used in this white paper are provided in Appendix C. The quality rating for each clinical study is listed in the Master Clinical Table, Appendix D.

Two studies, both of low quality, assessed the relationship between food-additive phosphate and, carotid intima-media thickness (IMT) and bone mineral density (BMD) (see Section "Food-additive phosphate, target organs, and biomarkers" for further details). The relationships between TP content in the diet and measures of bone or cardiovascular health were studied further in 13 publications. Based on the study designs and on the definitions used in this white paper, 12 of the studies provided evidence of low quality, and only one study was classified as high quality (see Section "Total dietary phosphorus, target organs, and biomarkers" for further details).

Food-additive phosphate, target organs, and biomarkers. Three clinical studies evaluated associations of food-additive phosphorus on target organs or biomarkers.

Itkonen and others (2013) conducted a cross-sectional analysis of randomly selected healthy adults from the Population Register Centre in Finland to determine whether dietary phosphorus intake (including TP, food-additive phosphate, and energy-adjusted TP [eTP]) are associated with higher carotid IMT and to determine whether high dietary phosphorus intake is a CVD risk factor in a general population. A total of 546 adults (176 males and 370 females) from Finland, with an average age of 41.9 ± 2.8 y were selected for the analysis. Subjects who had full nutrition, IMT, background, and biomarker data were included. Habitual dietary intake data were collected by using a 3-d FFQ, and nutritional data were calculated using a computer-based program based on the Fineli® Finnish food composition database. Carotid IMT was measured by ultrasonography, and biomarker measurements were assessed from 12-h fasting blood samples. Associations among TP, food-additive phosphate, and eTP intakes and IMT were tested by analysis of covariance between (1) all subjects, (2) males, (3) females, and (4) in between-group quintiles.

The results demonstrated that low-density lipoprotein cholesterol to high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio, eGFR, glycosylated hemoglobin A1c (HbA1c%), energy intake, total and saturated fat intake, calcium, and vitamin D intake were significantly higher with higher TP intake. The analysis of food-additive phosphate intake demonstrated that LDL-C/HDL-C ratio, serum triglycerides, eGFR, HbA1c%, TP, and energy intake were significantly and directly associated with changes in food-additive phosphate intake. There were no significant associations of food-additive phosphate with plasma FGF-23 ($P = 0.499$), serum intact-parathyroid hormone (iPTH) ($P = 0.313$), serum 25(OH)D concentrations ($P = 0.418$), or in calcium-to-phosphate (Ca:P) ratios ($P = 0.266$), but serum inorganic phosphorus concentrations were negatively associated with food-additive phosphate intake ($P = 0.006$). Energy intake and total and saturated fat intake were significantly lower when eTP intake was higher. Calcium, vitamin D, and TP intakes were positively associated with eTP intake. Serum iPTH concentrations were lower, and serum 25(OH)D concentrations were higher with higher eTP intake. Ca:P ratios were lower with lower eTP intake.

There were no statistically significant associations between IMT and TP, eTP, or food-additive phosphate intakes in males ($P > 0.05$). The results for all subjects, females, and in between-group analysis suggested trends in the associations of TP, eTP, and food-additive phosphate with IMT, some of which were statistically significant. For example, a significant positive linear trend occurred between eTP and IMT among all subjects ($P = 0.039$) and in between-group comparison of females in the 2nd and 5th quintiles ($P = 0.034$). There was a significant association between TP intake and IMT when looking at between-group comparison

in the 1st and 5th quintiles females ($P = 0.035$). A significant positive linear trend was also observed with food-additive phosphate intake and IMT among all subjects and in females ($P = 0.022$ and 0.045, respectively). Based on the positive linear trends in associations among eTP and food-additive phosphate intake with IMT in healthy, middle-aged Caucasian population, and significant higher IMT in females with the highest TP intake, the authors recommended further investigation into the potential association of TP and food-additive phosphate with CVD risk in the general population.

Tucker and others (2006) conducted a cross-sectional study to evaluate the association of consumption of cola beverages containing caffeine and phosphoric acid (H_3PO4), with BMD. A total of 2538 persons (1125 males [mean age: 59.4 ± 9.5 y] and 1413 females [mean age: 58.2 ± 9.4 y]) from the Framingham Osteoporosis Study who completed an FFQ were evaluated. BMD assessments of the right hip and lumbar spine were performed by dual-energy X-ray absorptiometry (DEXA) bone density scans. The mean daily dietary calcium intakes for all subjects (approximately 800 mg/d for the men and approximately 1000 mg/d for the women) were lower than the current recommendation of 1200 mg/d. Subjects tended to be overweight, former smokers, and moderate consumers of alcohol. Cola consumers had significantly lower intakes of calcium and lower Ca:P intake ratios (for both total and dietary calcium) than individuals who did not consume colas. The mean intake of carbonated beverages was 6 servings per week for the men and 5 servings per week for the women. Cola was the most commonly selected carbonated beverage for both men and women (5 and 4 servings per week, respectively), with women equally likely to consume caffeinated and noncaffeinated cola. There was an association between reduced BMD in the hip and cola consumption in women. However, there was no significant association between noncola carbonated beverage consumption with BMD for either men or women; the same was observed for men who consumed caffeinated cola.

No significant associations of caffeinated cola beverage consumption with spine BMD were observed for either men or women, even with additional analyses of subgroups of cola beverages (sugared cola, decaffeinated cola, and diet cola). However, in women, significant negative linear associations between consumption of caffeinated colas and BMD were observed at each of the hip sites ($P < 0.001$ for total hip, femoral neck, and Ward's area, and $P < 0.01$ for trochanter). This observation was evident even after adjustment for potential confounding variables (calcium intake and caffeine content). There was a significant dose–response relationship between the amount of cola intake and lower femoral neck BMD (differences ranged from 2.1% to 5.4%). In summary, although the results from this study showed that intake of cola beverages (but not of other carbonated soft drinks) is associated with low BMD in women, they did not demonstrate a clear association of differences in BMD with the amounts of phosphorus consumed, with Ca:P intake ratios or with the quantity of phosphoric acid in carbonated drinks.

A 30-d, randomized, crossover study evaluated the effects of substituting cola beverages for milk in the presence of a low-calcium diet in 11 healthy men (age: 22 to 29 y) (Kristensen and others 2005). The study was designed to evaluate the differences in serum concentrations of phosphate, calcium, 1,25(OH)2D, osteocalcin, BALP, PTH, C-telopeptides (CTX), and urine levels of cross-linked N-telopeptides (NTX) after replacing milk with a cola beverage. The study consisted of two 10-d treatment periods where subjects consumed either 2.5 L/d of a cola or semiskimmed milk beverage, separated by a 10-d washout period. Phosphorus and calcium contents of diets were calculated using a Danish computerized nutrient database. During the milk period, the average intakes of calcium and phosphorus were 3500 mg/d and 3640 mg/d, respectively (Ca:P = 0.96). Milk contributed 2375 mg phosphorus per day. During the cola period, the average intakes of calcium and phosphorus were 470 mg and 1690 mg, respectively (Ca:P = 0.28). Cola contributed 425 mg phosphorus per day. The serum concentration of phosphate was significantly increased after milk consumption compared with consumption of the cola beverage ($P < 0.001$). During the period of cola consumption, there were statistically significant increases in serum PTH ($P = 0.020$), osteocalcin ($P = 0.014$), and 1,25$(OH)_2$D ($P = 0.019$). There were no statistically significant changes in BALP after milk or cola consumption. Measures of bone resorption, including serum CTX concentration and urinary NTX excretion differed between the 2 treatments ($P < 0.001$). Both CTX concentration and urinary NTX excretion increased after the cola consumption, although not statistically significant, whereas significant decreases were seen after milk consumption ($P < 0.001$ and $P = 0.024$ for CTX and NTX, respectively).

The authors concluded that after a short-term low Ca:P diet where cola was substituted for milk, there were significant increases in the biochemical markers of bone turnover compared with an isoenergetic intake of 2.5 L milk with the same low-calcium diet. The study illustrated the potential health risk of inadequately low calcium intake and a low Ca:P ratio.

In summary, these 3 publications exemplify the difficulty in identifying a direct effect of food-additive phosphorus consumption on target organs or biomarkers. Itkonen and others (2013) analyzed the association between IMT and dietary phosphorus by evaluating TP and food-additive phosphates and did not find any significant associations. Only the between-group and subgroup analyses revealed some differences that suggested that changes in IMT may be associated with higher phosphorus intake. A significant positive linear trend was present only between food-additive phosphorus intake and IMT in an analysis of subgroups of women. The study by Tucker and others (2006) revealed the negative impact of cola on BMD, especially in postmenopausal women which resulted in a significant negative linear association of cola consumption with differences in the mean hip BMD. Women who consumed one cola drink or more daily were reported to have 3.7% to 5.4% lower mean hip BMD than compared with women who consumed less than one serving of cola per month. The association of changes in BMD was associated with a dose–response relationship with cola intake and was consistent across all types of cola. However, the relationship of phosphorus consumption and BMD was not elucidated in this study. The results of a short-term study that evaluated replacing milk with cola beverages suggested potential health risks of biochemical markers of bone turnover associated with low Ca:P intake. In 2 studies, negative associations between phosphorus intake and IMT or lower BMD were primarily manifested in women. The basis of these sex-associated observations is not clear and will only be resolved with further research.

A study evaluating the association of biomarkers of bone metabolism after a short-term low Ca:P diet where cola was substituted for milk showed significant increases in the biochemical markers of bone turnover compared with an isoenergetic intake of 2.5 L milk with the same low-calcium diet (Kristensen and others 2005).

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake in the general population included, variously, those inherent in studies of observational design as well as the selection of subjects likely to be healthier than average. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Total dietary phosphorus, target organs, and biomarkers. The literature search identified 12 primary research publications that evaluated the association of total dietary phosphorus and target organs or biomarkers. Four studies evaluated the association of total dietary phosphorus with cardiovascular outcomes (Shuto and others 2009; Alonso and others 2010; Yamamoto and others 2013; Kwak and others 2014); 8 with bone mass outcomes (Teegarden and others 1998; Jones and others 2000; Méndez and others 2002; Bounds and others 2005; Yin and others 2010; Ito and others 2011; Lee and others 2014). A summary of the studies is presented in Table 4.

Biomarkers of CVD. Kwak and others (2014) evaluated whether dietary calcium and phosphorus intakes and serum concentrations were associated with the prevalence of CAC in subjects without a history of CKD or CVD in 23652 healthy Korean adults (age: 40.8 ± 7.3 y). Subjects completed a self-administered FFQ and cardiac computed tomography was used to determine each subject's CAC scores. The median (interquartile range) dietary calcium and phosphorus intakes were 339.3 mg/d and 759.2 mg/d, respectively. The mean (SD) serum calcium concentration, median (interquartile range) serum phosphorus concentration, and CP-P were 9.41 mg/dL, 3.5 mg/dL, and 33.3 mg^2/dL^2, respectively. CAC score ratios reflected the degree of CAC and were calculated using multinomial logistic regression models that adjusted for age and sex. There was no association between dietary phosphorus or dietary calcium intake with CAC score ratios. However, serum calcium and phosphorus concentrations and CP-P were significantly associated with the CAC score ratios. Adjusting for vitamin D serum levels among 6148 participants did not change the results. In summary, there was no association of dietary phosphorus or calcium intakes with CAC score ratios, but high levels of serum calcium and phosphorus and high CP-Ps were associated with an increased prevalence of CAC, regardless of serum vitamin D levels.

Yamamoto and others (2013), investigated the association of dietary phosphorus with LVM in 4494 subjects with no baseline CVD, drawn from the MESA. The mean age of subjects was 61.6 y. Dietary phosphorus intake was estimated from FFQs, and the LVM was measured using magnetic resonance imaging. Regression models were used to determine associations of estimated dietary phosphorus with LVM and LVH. Men consumed more dietary phosphorus than women (mean: 1167 mg/d compared with 1017 mg/d). After adjusting for height, weight, age, and race, each 20% increase in estimated dietary phosphorus intake was associated with an estimated 0.42 g greater LVM (95% CI: 0.14 to 0.70 g) and with a higher mass-to-volume ratio (0.006 g/mL; $P = 0.02$), but not with differences in left ventricular end-diastolic volume or stroke volume. Further adjustments strengthened the association. When adjusted for differences in sex, higher estimated dietary phosphorus was associated with greater LVM, and the association was stronger among women (particularly postmenopausal women).

Alonso and others (2010) evaluated the association of phosphorus intake with BP and risk of hypertension in an analysis of data from 13444 subjects who participated in 2 large observational cohorts in the U.S. (from the ARIC and the MESA study; age: 45 to 64 y). Dietary data were assessed in the ARIC using a 66-item FFQ and in the MESA using a 120-item FFQ. Nutrient intake was adjusted for total energy intake and categorized into sex-specific quintiles. The average phosphorus intake was similar in the 2 cohorts (1084 mg/d in the ARIC, 1103 mg/d in the MESA). The results demonstrated that higher phosphorus intake was significantly associated with lower levels of systolic and diastolic BP in both cohorts, even after adjustment for potential confounders (that included BMI, smoking, physical activity, and eGFR). In the ARIC cohort, systolic BP was 2.3 mm Hg (95% CI: 1.3, 2.3) lower in highest quintile of phosphorus intake than in the lowest; results in the MESA cohort were similar (−2.3 mm Hg [95% CI: −4.2, −0.5] lower in the highest than lowest quintile of phosphorus intake). There were smaller differences in diastolic BP among extreme quintiles in the ARIC: −0.9 mm Hg (95% CI: −1.5, −0.3) and the MESA: −1.4 mm Hg (95% CI: −2.3, −0.4). During an average follow-up of 6.2 y (7.1 y in the ARIC, 3.8 y in MESA), 3345 incident cases of hypertension (2400 in the ARIC, 945 in MESA) were identified. Individuals in the top quintile of phosphorus intake had approximately a 10% lower risk of hypertension than those in the lowest, after adjustment for potential confounders. An increase in phosphorus intake was associated with lower risk of hypertension in both men and women. The main source of dietary phosphorus in both cohorts was dairy products (31% in the ARIC, 29% in MESA), followed by fish, red meat, white bread, poultry, and whole-grain bread, in different proportions in the 2 studies. Only higher phosphorus intake from dairy products, but not other dietary sources, was associated with lower levels of systolic BP and lower risk of hypertension.

Shuto and others (2009) performed a double-blind crossover study to investigate the effect of dietary phosphorus loading on endothelial function in 11 healthy men (age: 21 to 33 y). A description of the design of the study is in Section "Other associations and analyses". The subjects were alternately served breakfast meals containing 400 or 1200 mg of phosphorus and a standard dinner. Serum phosphorus was measured over 8 h after the meals; peak concentrations for the 400-mg diet occurred at 6 h (3.9 ± 0.12 mg/dL) and for the 1200-mg diet at 2 h (5.0 ± 0.11 mg/dL). The serum phosphorus levels after ingestion exceeded the normal range (that is, were >4.5 mg/dL) in 8 of 11 subjects after the 1200-mg diet, while the serum phosphorus levels did not change significantly with the 400-mg meal (3.66 ± 0.2 mg/dL) and stayed within the normal range (2.5 to 4.5 mg/dL). Serum iPTH levels tended to decrease after breakfast, but were significantly higher after the 1200-mg meal than after the 400-mg meal. Other serum chemistry measurements were not significantly different between the 2 meals. The effect of dietary phosphorus loading on endothelium-dependent vasodilation was evaluated by assessing postprandial changes in the percent flow-mediated dilatation (%FMD). There was a significant decrease in %FMD, 2 h after the 1200-mg meal with a significant negative correlation between serum phosphorus levels and %FMD (Spearman's coefficient $r = -0.42$; $P = 0.006$) that normalized after at least 24 h. No significant correlation between serum phosphorus level and %FMD was observed after the 400-mg meal. The authors suggest that acute postprandial hyperphosphatemia may cause endothelial dysfunction and so contribute to associations between serum phosphorus concentration and mortality and morbidity observed in other studies (Tonelli and others 2005; Dhingra and others 2007).

Table 4–Summary of studies evaluating association of dietary phosphorus and biomarkers

Study reference	*N*	Study design	Outcome measure	Results
Cardiovascular biomarkers				
Kwak and others (2014)	23652 healthy Korean adults	Observational study, cross-section analysis	Coronary artery calcification	No association with dietary P.
Yamamoto and others (2013)	4494 healthy subject with no CVD	MESA (observational study)	LVM, LVH	Dietary P associated with increases in LVM and LVH.
Alonso and others (2010)	13444 healthy subjects	MESA and ARIC (observational studies)	SBP, DBP, hypertension	Dietary P associated with reduced SBP, DBP, and hypertension.
Shuto E and others, 2009	11 healthy men	Double-blind, crossover trial	Vascular endothelial dilation measured by %FMD	Dietary P associated with acute decrease in %FMD.
Bone metabolism biomarkers				
Haraikawa and others (2012)	193 healthy young Japanese adults	Observational trial	BALP activity	Dietary P negatively correlated with serum BALP.
Ito and others (2011)	441 healthy Japanese women	Observational trial	BMD	Ca:P was associated with distal radius BMD.
Lee and others (2014)	4935 healthy Korean adults	Observational trial	BMD	Ca:P was associated with BMD.
Yin and others (2010)	216 mostly white adolescents in Tasmania	Observational trial	BMD	Maternal dietary intake during pregnancy of phosphate associated with lumbar spine BMD of 16-y-old adolescents.
Bounds and others (2005)	52 white children	Observational trial	BMD and BMC	Dietary P intake directly associated with BMD and BMC but in female sex, dietary P was negatively associated with BMC.
Méndez and others (2002)	47 postmenopausal women	Observational trial	BMD	No association of P intake and BMD.
Jones and others (2000)	173 8-y-old children	Observational trial	BMD	Maternal dietary P associated with lumbar spine BMD.
Teegarden and others (1998)	215 white women	Observational trial	BMD and BMC	Dietary P intake associated with BMD and BMC.

%FMD, percent flow-mediated dilation; ARIC, Atherosclerosis Risk in Communities Study; BMC, bone mineral content; BMD, bone mineral density; Ca:P, calcium to phosphate ratio; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MESA, Multi-Ethnic Study of Atherosclerosis; P, phosphate; SBP, systolic blood pressure.

In summary, 4 studies examined the relationship between dietary phosphorus intake with cardiovascular outcomes, with some reporting beneficial associations, others adverse associations, and one finding no association, depending on the specific variables evaluated and the design of each study. Kwak and others (2014) showed that dietary phosphorus was not associated with increased risk of CAC. The results from a cross-sectional analysis of data from 2 large cohorts demonstrated that Alonso and others (2010) showed a possible protective effect of high phosphorus intake, higher phosphorus intake was significantly associated with lower levels of systolic and diastolic BP in older adults. They also suggested that the high source of phosphorus intake in the form of dairy products might lower the risk of hypertension. However, Yamamoto and others (2013) determined that higher dietary phosphorus intake was associated with greater LVM index in both men and women and with greater risk in women. When evaluating the contribution of dietary nutrients in regulating serum BALP, they also noted that the association was independent of serum phosphate concentration or dietary phosphorus intake, even when men consumed more than women, when evaluating the contribution of dietary nutrients in regulating serum BALP. A small study by Shuto and others (2009) in young healthy adult men illustrated that high dietary phosphorus intake and high serum phosphorus levels were associated with reduced vascular endothelial function. Based on the study designs and on the definitions used in this white paper (Appendix C), 3 of the studies (Alonso and others 2010; Yamamoto and others 2013; Kwak and others 2014) provided evidence of low quality, and one (Shuto and others 2009) was classified as high quality. Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake in the general population included those inherent in studies of observational design and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Biomarkers of bone metabolism. A study by Haraikawa and others (2012) evaluated the contribution of dietary nutrients in regulating serum BALP activity. A total of 193 (97 males and 96 females) healthy young Japanese volunteers with an average age of 22.1 ± 1.8 y were enrolled in an observational study. Fasting blood samples were obtained. Serum biochemical parameters, including serum ALP, BALP, osteocalcin, and FGF-23, were measured. Dietary nutrient intakes were measured based on 3-d food records before the day of blood collections. Trained personnel reviewed the food records and the nutrient content was determined using proprietary software. Daily intakes (mean ± SD) were as follow: phosphorus 1059 ± 302 mg/d, energy 2078 ± 555 kcal/d, calcium of 556 ± 223 mg/d, and vitamin D of 5.8 ± 4.8 μg/d. There was a significant negative correlation between phosphorus intake and serum BALP activity ($r = -0.226$;$P = 0.002$). Serum BALP activity was also significantly correlated with serum phosphorus concentrations ($r = -0.165$; $P = 0.022$). In addition, serum phosphorus concentration was significantly correlated with dietary phosphorus intake ($r = 0.183$; $P = 0.011$). Serum BALP was significantly and negatively correlated with calcium intake ($P = 0.01$) and was positively correlated with serum FGF-23 ($P = 0.008$) and with serum ALP ($P < 0.001$).

Ito and others (2011) evaluated the association of habitual phosphorus and calcium consumption and the Ca:P intake ratio with BMD in 441 young Japanese women (age: 18 to 22 y). The average Ca:P intake ratio in these women was assumed to be lower (0.50 [475/955]) than in young Western women (0.70 to 0.76

[802 to 1056/1056 to 1411]). In addition, PTH and 25(OH)D were examined in 214 of the 441 subjects. A single 24-h urine sample was collected. Dietary habits during the preceding month were assessed using a self-administered diet history questionnaire. Estimates of dietary intake for energy and nutrients, including phosphorus and calcium, were calculated using an *ad hoc* computer algorithm for the diet history questionnaire based on the Standard Tables of Food Composition in Japan. Multiple regression analysis (after adjustment for postmenarcheal age, BMI, and physical activity) showed that calcium intake and the Ca:P intake ratio independently had positive and significant associations with BMD in the distal radius.

Lee and others (2014) evaluated whether dietary calcium and phosphorus intakes and dietary Ca:P ratio were associated with bone mass in 4935 Korean adults. Dietary calcium and phosphorus intakes of the participants were estimated using 24-h dietary recall. Bone mass densities for the whole body, femoral neck, and lumbar spine were measured by DEXA scans. The authors reported a positive correlation between dietary calcium intake ($P = 0.046$), and Ca:P intake ratio ($P = 0.041$), and femoral neck BMD in men older than 50 y. In men aged younger than 50 y, dietary calcium and Ca:P intake were positively related to lumbar spine BMD and negatively related to whole body BMD. There was also a small but significant positive correlation between dietary calcium ratio and femoral neck and whole body BMD in premenopausal women. After adjusting for covariates (including age, income, education, residential area, alcohol, smoking, physical activity, energy intake per day, the presence of dietary supplements, total duration of breast-feeding in women, BMI, and serum ALP, ferritin, and vitamin D concentrations), dietary calcium intake and Ca:P intake ratio were still positively related to BMD in the femoral neck of men aged older than 50 y, and in premenopausal women, dietary calcium intake also showed positive associations with the whole body BMD. These findings suggest that increased calcium intake and high Ca:P intake ratio might have beneficial effects on bone mass in the Korean population.

Yin and others (2010) conducted a prospective observational study that evaluated 216 mostly white adolescents in Australia (Tasmania) to describe the association between maternal dietary intake during pregnancy and bone mass of the offspring at age 16 (16.2 ± 0.4 y). Dietary intake during the 3rd trimester of pregnancy was measured with a self-administered FFQ completed shortly after birth. The dietary variables from the FFQs were converted to nutrient density and the association between maternal diet and bone mass in the adolescents was measured as BMD of the femoral neck, lumbar spine, and total body by DEXA scan. Neither univariate nor multivariate analysis demonstrated that maternal nutrients (protein, calcium, or phosphorus density) intakes were associated with total body BMD in the 16-y-old adolescents. After adjustment for potential confounding factors (sex, weight at age of 16 y, sunlight exposure in winter, sports participation, current calcium intake, Tanner stage at age of 16 y, ever breast-fed, smoking during pregnancy, maternal age at the time of childbirth), there was a positive association between phosphorus, calcium, and magnesium density intake during pregnancy and lumbar spine BMD (all $P < 0.05$) of the adolescents. In addition, milk intake during pregnancy was positively associated ($P < 0.05$) with lumbar spine BMD of the 16-y-old adolescents. The results suggest that maternal intake of milk during the 3rd trimester of pregnancy may be predictive of the offspring's BMD at age of 16 y.

Bounds and others (2005) conducted a prospective cohort study that evaluated the association of nutrient intake with bone mineral content (BMC) and BMD in 52 white children (25 boys, 27 girls). Longitudinal nutrient intake (between 2 mo and 8 y) was collected on 9 occasions from 3 d of dietary information (2 d from food records and 1 d from 24-h recall). BMC and BMD measurements of the 52 children (at 8 y old) and their mothers were performed by DEXA scan. Multivariate models were used to predict the children's total BMC and BMD. Phosphorus intake ($r = 0.33$; $P \leq 0.05$), energy($r = 0.41$; $P \leq 0.05$), calcium ($r = 0.32$; $P \leq 0.05$), protein ($r = 0.37$; $P \leq 0.05$), magnesium ($r = 0.40$; $P \leq 0.05$), and zinc ($r = 0.343$; $P \leq 0.05$) were significantly and positively correlated with total BMC. Phosphorus ($r = 0.30$; $P \leq 0.05$), energy ($r = 0.30$; $P \leq 0.05$), protein ($r = 0.33$; $P \leq 0.05$), and magnesium ($r = 0.32$; $P \leq 0.05$) were also significantly correlated with total BMD. To analyze the children's longitudinal bone mineral indexes, DEXA scans were performed at 6 and 8 y of age. The children's bone mineral indices showing the changes in bone measures over time were highly significant for total BMC ($r = 0.86$; $P < 0.0001$) and total BMD ($r = 0.92$; $P < 0.0001$). The only significant negative predictor of total BMC and BMD was female sex at the age of 8 y.

Méndez and others (2002), conducted a prospective, observational study that enrolled 47 postmenopausal women (45 to 63 y) in northern Mexico. Dietary intake was assessed twice, by 24-h recall, and BMD measurements of the forearm and heel were assessed by DEXA scan. The dietary calcium intake was 1128 ± 522 mg/d with 70% of the women meeting the National Research Council recommended dietary allowances (RDAs) of calcium consumption of 800 mg/d but only 15% consumed the 1500 mg/d dietary calcium intake recommended by the National Institutes of Health. The mean dietary intake of phosphorus was 1579 ± 525 mg/d, resulting in a 1:1.8 Ca:P molar ratio (a 1:1 molar ratio of Ca:P is recommended for most age groups). The RDA for protein in this age group is 50 g, and the average intake for the women was 61 g/d consisting of a high intake of animal protein. The fiber intake was also higher at 33 g/d than the population average (U.S. mean fiber intake is approximately 12 g/d). In this study, there was a significant association between calcium intake and calcium excretion ($r = 0.29$; $P = 0.05$). There was a negative correlation of both urinary calcium ($r = –0.31$; $P = 0.03$) and calcium/creatinine ratio ($r = –0.39$; $P = 0.008$) with BMD in the forearm. However, no relationship of calcium or phosphate intake with BMD was detected, although the calcium intakes were below that recommended by the National Institutes of Health for postmenopausal women.

Yin and others (2010) conducted a prospective observational study in 173 children (8 y old) from Australia (Tasmania), which evaluated the association between maternal diet during the 3rd trimester of pregnancy and bone mass. Bone mass (BMC and BMD) at the lumbar spine and femoral neck was measured by DEXA scans. Nutrient intake during pregnancy was high compared with previously reported mean dietary intakes, with calcium intake at 1905 mg/d and phosphorus at 2767 mg/d. Results for BMC and BMD were very similar; therefore, only BMD analyses were included in the publication. Significant associations of nutrient intake during pregnancy with BMD were seen for the following nutrients: phosphorus and magnesium intake with BMD at the femoral neck; phosphorus, potassium, magnesium, and fat intake with BMD at the lumbar spine; and potassium, magnesium, protein, and fat intake with total body BMD. After adjusting for dietary variables and using linear regression models, the only statistically significant associations detected for minerals were between phosphorus and fat intakes and lumbar spine BMD. Associations

between food intake (vegetables, fruit, milk, meat, and fish) during pregnancy and BMD in 8-y-old children showed that only milk was significantly associated with femoral neck BMD.

Teegarden and others (1998) conducted an observational study of 215 white women (age: 18 to 31 y) using anthropometric measurements to examine the effects of calcium, protein, and phosphorus intake on bone mass at various sites. Analyses of anthropometric and bone mineral measurements revealed positive correlations of protein, calcium, and phosphorus intakes with radius and spine BMD as well as with spine BMC. Multivariate and univariate regression analyses showed a complex relationship between calcium and phosphorus or protein (and their ratios) and total-body and spine BMD or BMC. The authors concluded that increasing phosphorus intake had a positive effect on BMD and BMC (total-body and spine) combined with low calcium intake (600 mg/d). However, as calcium intakes increased (up to 1400 mg/d), a high phosphorus intake (1800 mg/d) was detrimental to BMD and BMC (total-body and spine). Absolute intakes of calcium and phosphorus as well as dietary the Ca:P molar ratio had significant effects on the spine and total-body BMDs and BMCs, and a 1:1 Ca:P molar ratio may not be optimal to maximize peak bone mass in individuals in the age range evaluated in this study.

Eight studies concentrated on the associations of biomarkers of bone metabolism with dietary nutrients, including phosphorus and calcium intake. The results of these studies showed that dietary phosphorus was associated with changes in biomarkers of bone metabolism in different populations of individuals. Haraikawa and others (2012) determined that serum phosphorus concentrations were significantly correlated with dietary phosphorus intake in regulating serum BALP. In the study by Ito and others (2011), the Ca:P intake ratio had positive and significant association with BMD in the distal radius of Japanese women. Teegarden and others (1998) showed that protein, calcium, and phosphorus intakes positively correlated with radius and spine BMD as well as spine BMC in young women. Bounds and others (2005) showed that longitudinal nutritional intakes (dietary data collected at various points from children 2 to 8 y old) of phosphorus, energy, calcium, protein, magnesium, and zinc were positively correlated with total BMC. However, female sex was negatively associated with both BMC and BMD at this age. Jones and others (2000) showed that there were significant associations of intakes of various nutrients during pregnancy with the BMC or BMD in 8-y-old children. However, after adjusting for different dietary variables, only phosphorus and fat intakes remained significantly associated with lumbar spine BMD. Lee and others (2014) showed a positive correlation of dietary calcium intake and femoral neck BMD in older men and premenopausal women but there was no association of dietary phosphorus intake with BMD. Brot and others (1999) showed that a higher dietary Ca:P ratio was associated with higher bone mass. However, Méndez and others (2002) were not able to find a relationship of calcium or phosphate intake with heel and forearm BMD in a study of postmenopausal women from Mexico. Yin and others (2010) also reported that maternal phosphorus and calcium intake were not associated with whole body BMD in 16-y-old adolescents, but there was a positive association with lumbar spine BMD, which might be attributed to nutritional factors in milk intake during pregnancy. The possibility that maternal nutrition, especially dietary phosphorus and fat influences skeletal development of the offspring, was also described by Jones and others (2000). The mechanism for high phosphorus intake and the association with phosphorus serum levels and CVD or bone mass outcomes remain incompletely understood as evident from the publications described above. Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included those inherent in studies of observational design, the limited reliability of the methods used for quantification of dietary phosphorus intake, and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Total dietary phosphorus, regulatory hormones, and other physiological outcomes

The literature search identified 19 published primary clinical research studies that evaluated the association of total dietary phosphorus and physiologic outcomes that consisted of changes in serum PTH or FGF-23 concentrations, or changes in calcium disposition in healthy adults and children. Three studies specifically evaluated the association of physiological outcomes with food-additive phosphorus, 8 studies evaluated the association of physiological outcomes with total dietary phosphorus, and 8 studies evaluated the association of physiological outcomes with phosphorus load. Associations of serum phosphorus concentrations with physiologic outcomes are discussed in the Section "Serum phosphorus concentration, regulatory hormones and other physiological outcomes". The quality rating for each clinical study is listed in the Master Clinical Table, Appendix D.

Food-additive phosphate, regulatory hormones, and other physiological outcomes. Three studies evaluated the effects of food-additive phosphates on changes in PTH concentrations or on physiological outcomes. A summary of the description of methods used to evaluate food-additive phosphorus consumption in the studies is provided in Table 5.

An observational study evaluated whether NP or food-additive phosphorus were associated with effects on biomarkers of calcium metabolism and bone metabolism in 147 adult women, 31 to 43 y of age (Kemi and others 2009). Women who were habitual consumers of carbonated beverages were randomly selected in Finland. Fasting blood samples were obtained between 7.30 a.m. and 9.15 a.m. after a 12-h overnight fast. Participants maintained a 4-d food record, from which total dietary intake of phosphorus and the consumption of NP (milk and cheese, excluding processed cheese) and food-additive phosphorus (processed cheese) sources was calculated. Participants were divided into groups according to natural or food-additive phosphorus-containing food consumption and into quartiles according to their TP intake. The investigators analyzed associations of the extreme quartiles (Quartile 1 and Quartile 4) of TP intake. Mean phosphorus intakes were 961 $\pm$ 22 mg/d and 1956 $\pm$ 48 mg/d in the 1st and 4th quartiles, respectively. The mean serum PTH concentration in all subjects was 30.6 ng/mL ($\pm$1.3). Mean serum PTH concentrations were significantly greater ($P = 0.048$) and the mean serum ionized calcium concentrations were significantly lower ($P = 0.016$, analysis of covariance) in women with the highest compared with the lowest quartiles of total dietary phosphorus intake. Serum PTH was greater in subjects who consumed processed cheese that had high amounts of food-additive phosphorus than in those who did not consume processed cheese, but the results were not statistically significantly different. The results demonstrated that higher total habitual dietary phosphorus intake was associated with higher serum PTH levels and lower serum ionized calcium concentrations, even after total dietary calcium intake was equalized. The authors considered

Table 5–Summary of diets in clinical studies evaluating food-additive phosphates and physiological outcomes

Study reference	Study population	Adjustments	Methods to determine dietary intake	Duration
Kemi and others (2009)	Randomly selected group of 147 healthy premenopausal women in Finland	Calculations of mean serum calcium, included covariate of serum PTH and excluded sodium intake, age, energy intake, and body weight.	Habitual dietary intake calculated with the Unilever Dietary Analysis Computer Program based on the food composition database (Fineli) of the Finnish National Public Health Institute. Nutrient contents of all foods based on the food composition database (Fineli) of the Finnish National Public Health Institute.	4 d
Heaney and Rafferty (2001)	30 women (mean age 31.4 ± 5.6 y) who were habitual consumers of carbonated beverages (680 mL [two 12-oz cans] daily)	No adjustments made	Phosphorus was analyzed by an autoanalyzer method based on Fiske and Subba Row.	1 mo
Mazariegos-Ramos and others (1995)	228 children; 123 recruited from primary medical care facilities and 105 from schools; 57 case subjects, 171 control subjects	No adjustments made	A masked investigator interviewed children and their mothers to determine the number of bottles consumed per week (1 bottle = 375 mL) of soft drink with phosphoric acid (Coca-Cola or Pepsi-Cola).	1 wk; 17 children evaluated 30 d after discontinued consumption of soft drinks

PTH, parathyroid hormone.

that in the habitual diets of healthy individuals, foods containing food-additive phosphorus had more "harmful effects" on calcium metabolism than foods containing NP. These harmful effects were seen as higher serum PTH concentrations among those who consumed food-additive phosphorus-containing foods. This difference may have been due to the different bioavailability of P from food-additive phosphorus and NP sources. In addition, the mean serum PTH was almost 2-fold higher and the mean serum ionized calcium was lower among participants whose habitual TP intake was the highest compared with those whose intake was the lowest.

The authors concluded that higher habitual total dietary phosphorus intakes were associated with higher mean serum PTH and lower mean serum ionized calcium concentrations. In the habitual diets of a randomly selected sample of women, the authors suggested that food-additive phosphorus might affect bone more negatively than other phosphorus sources, as indicated by higher mean serum PTH concentrations among participants consuming food-additive phosphorus-containing foods. The effects of NP from milk and cheese, excluding processed cheese, on serum PTH were the opposite of those of food-additive phosphorus-containing foods, probably due to higher calcium content in these foods. This was considered important new information as the consumption of processed foods has increased during the last decades, which in turn has increased phosphorus intake from food-additive phosphorus.

The acute effects of urinary calcium loss after consuming carbonated beverages of various compositions were evaluated in 32 adult women in Finland (Heaney and Rafferty 2001). The healthy women volunteers were 31 to 43 y of age, mean age of 31.4 ± 5.6 y, habitual consumers of carbonated beverages who consumed at least two 12-ounce cans (680 mL) of carbonated beverages daily. Four carbonated beverages were tested: 2 with caffeine and 2 without; 2 contained phosphoric acid as the acidulant and 2 contained citric acid. The study included 1 neutral control (water) and 1 positive control (skim or chocolate milk). The study employed an incomplete random block design in that 5 beverages were consumed by each woman (water, both of the cola beverages, 1 of the milks, and 1 of the 2 citric acid-containing beverages). Serving sizes of the carbonated beverages and water were 567 and 340 mL for the milk beverages. Beverages were consumed with a light breakfast after an overnight fast; no other foods were ingested until urine collection was complete. Urine pH, titratable and total acidity, sodium, creatinine, and calcium were measured in the 2-h (morning) fasting and 5-h postbeverage urine specimens. The sequence of tests in each woman was arranged in a 1-wk cycle, so that the entire suite of 5 tests was completed in most subjects within 1 calendar month.

The greatest increases in urinary calcium excretion were observed after consuming milk beverages as the positive controls. Except for milk, there was little increase in urinary calcium excretion with the other beverages. Increases in urinary calcium excretion were greater after consuming the 2 caffeine-containing beverages ($P < 0.05$). Consumption of the beverages with phosphoric acid without caffeine produced no excess calciuria. There were no significant differences in urinary calcium excretion between the 2 acidulant beverages (phosphoric acid or citric acid). However, the 2 phosphoric acid-containing colas resulted in producing urine with the greatest acid excretion. The authors concluded that the added variables of acid (phosphoric or citric acid) and phosphorus seem to have produced no detectable effects on urine calcium excretion. This conclusion is supported by the finding that the caffeine-free cola containing phosphoric acid did not produce significant excess calciuria.

A case-controlled study was conducted to determine if consumption of at least 1.5 L/wk of soft drinks containing phosphoric acid was a risk factor for the development of hypocalcemia in children (Mazariegos-Ramos and others 1995). The study was designed as a case–control study with a ratio of 1:3, 51 cases to 153 controls. Cases were defined as children with serum calcium levels <2.2 mmol/L (8.8 mg/dL), and controls as individuals with serum calcium levels of at least 2.2 mmol/L. The study enrolled 57 children with serum calcium concentrations <2.2 mmol/L and

Table 6–Summary of diets in clinical studies evaluating dietary phosphorus and physiological outcomes

Study reference	Study population	Methods to determine dietary intake	Duration
Delgado-Andrade and others (2011)	20 healthy, male adolescents; Mean age: 12.4 ± 0.34 y	Two 7-d menus of content similar in energy and nutrients to a Spanish diet, and containing the same servings per day of the different food groups were created: a white diet free of foods in which the Maillard reaction develops during cooking practices (that is, frying, toasting, roasting) or food containing MRPs (bread crust or chocolate); and a brown diet rich in processed foods with an evidence of browning and rich in MRPs (that is, corn flakes, baked products, fried and breaded foods, chocolates). At end of each 14-d treatment period, assessed 3-d phosphorus balance by collecting 24-h urine and feces.	Two 14-d diet treatment periods separated by 40-d washout
Ito and others (2011)	441 young, healthy Japanese women (18 to 22 y); 214 women for assessment of PTH	Nutrient intake, including phosphorus and calcium, was calculated; methods not disclosed.	1 d: 24-h sampling period
Gutiérrez and others (2011)	1261 healthy male healthcare professionals age 40 to 75 y (mean 64 ± 9 y (in 1986) (from 51529 total subjects enrolled in the cohort)	A self-administered semiquantitative FFQ completed closest to the blood draw was used to assess average nutrient intake over the past year. FFQ inquired about the use of calcium supplements, vitamin D supplements, and multivitamins. Intake of specific dietary factors was computed from the reported frequency of consumption of each specified unit of food and from United States Department of Agriculture data.	1 d: 24-h sampling period
Kemi and others (2009)	147 healthy, premenopausal Finnish women, 31 to 43 y	Collected nutrient intakes with 4-d food record (included 3 weekdays and 1 d of the weekend). Nutritionist checked the 4-d food record with the participant. Calculated habitual dietary intakes with computer-based Unilever Dietary Analysis Program based on the food composition database (Fineli) of the Finnish National Public Health Institute.	1 d: 24-h sampling period
Obeid and others (2010)	53 healthy male and female subjects, mean ages 20.7 to 26.6 y	Two chilled liquid, 400-mL solutions, randomly assigned, with or without addition of 500 mg of phosphorus (mixture of potassium and sodium phosphate).	1 wk
López-Huertas and others (2006)	15 healthy volunteers; 8 men, 7 women, mean age of 28.7 ± 3.7 y	Stable isotopes administered: calcium carbonate as ^{42}Ca and ^{44}Ca administered orally and ^{43}Ca administered intravenously to estimate true fractional absorption of calcium. One of 5 drinks enriched with calcium from milk solids and 15.5% calcium from tricalcium phosphate [$Ca_3(PO_4)_2$] compared with drinks with different sources of calcium. Dietary intake was assessed at weeks 1 and 11 by using the diaries completed by the volunteers.	11 wk
Heaney (2000)	191 women, mean age of 48.7 ± 7.0 y	Diets were chemically analyzed. Duplicate weighed diets were prepared for each inpatient metabolic study for each subject. Calcium and phosphorus were measured in a hydrochloric acid solution of ashed diet by using atomic absorption spectrophotometry for calcium and the method of Fiske and Subbarow for phosphorus.	>20-y period
Brot and others (1999)	510 healthy Danish perimenopausal women, with amenorrhea for 3 to 24 mo; mean age 50.6 ± 2.8 y (45 to 58 y)	Phosphorus intakes recorded using 4- or 7-d dietary records in 488 women. All foods and beverages consumed daily were recorded, estimating quantities in household measures. All food records were analyzed for nutrients intake using Dankost Software (Version 1.3b), a program based on the official Danish food tables.	1 d

Ca, calcium; FFQ, food frequency questionnaire; MRP, Maillard reaction products.

171 control subjects. The mean age was 67.5 ± 29.3 mo for the case subjects and 67.5 ± 29.0 mo for controls. The case children consumed more soft drinks than the control. Of the 57 children in the case group, 38 (66.7%) drank more than 4 bottles of soft drink per week compared with only 48 (28%) of the 171 control children ($P < 0.001$). In all children, there was a significant negative correlation ($r = -0.41$; $P < 0.001$) between the serum calcium levels and the number of bottles of soft drink consumed each week. In a follow-up study in 17 children, 30 d after soft drink intake was discontinued, basal serum calcium levels were significantly increased from 8.7 ± 1.0 to 9.4 ± 0.6 mg/dL ($P < 0.003$) and phosphorus levels significantly decreased from 5.7 ± 1.3 to 4.7 ± 0.6 mg/dL ($P < 0.002$). The authors concluded that there is a causal relationship between ingestion of soft drinks containing phosphoric acid and hypocalcemia and suggested that this relationship should be explored in further studies.

In summary, only 3 studies were identified in the literature that evaluated the physiological effects associated with food-additive phosphorus. The quality of evidence is considered high for 1 study (Heaney and Rafferty 2001) and low for 2 studies (Mazariegos-Ramos and others 1995; Kemi and others 2009) based on the design of the studies as defined in Appendix C. The studies revealed the following:

- Greater total habitual consumption of diets with food-additive phosphorus was associated with greater serum PTH and lower serum ionized calcium concentrations in healthy women; the changes in both serum PTH and calcium levels were greater after consumption of foods containing phosphate food additives than from foods containing natural phosphates.
- Consumption of beverages with food-additive phosphorus (consisting of cola beverages) did not result in excess calcium excretion in the urine in healthy women but was associated with producing urine with greater acid excretion compared with other beverages.
- Consumption of large amounts of soft drinks that contained food-additive phosphorus in children was associated with reduced serum calcium levels (hypocalcemia).

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included those inherent in studies of observational design; the limited accuracy of the methods employed to determine true food-additive phosphate intake; and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Total dietary phosphorus, regulatory hormones, and other physiological outcomes. Eight published primary clinical research studies evaluated relationships between consumption of total dietary phosphorus and physiological outcomes. The diets in these studies were assessed for phosphorus content but were not specifically characterized as diets that consisted of food-additive phosphates. Studies are described in chronological order, with the most recent study described first. A summary of the methods used to evaluate food-additive phosphorus consumption in the studies is provided in Table 6.

The influence of habitual phosphorus and calcium consumption on BMD and urinary phosphorus excretion was evaluated in a cross-sectional analysis of a prospective study of 441 young healthy Japanese women, aged 18 to 22 y (Ito and others 2011). Serum PTH concentrations were also examined in this study which is described in more detail in Section "Total dietary phosphorus, target organs, and biomarkers". The results demonstrated that phosphorus intake, calcium intake, and the calcium/phosphorus intake ratio correlated positively only with urinary phosphorus excretion. Phosphorus and calcium intake and the Ca:P intake ratio had no relationship with urinary calcium. There was no association between serum PTH and phosphorus intake, calcium intake, or the calcium:phosphorus intake ratio.

A 2-wk, randomized, 2-period, crossover trial evaluated the effects of consuming diets rich in Maillard reaction products (MRPs) on phosphorus digestion and balance in 20 healthy male adolescents, aged 11 to 14 y (Delgado-Andrade and others 2011). MRPs are added to food to change the color and taste of foods. One diet was rich in MRPs (brown diet) and the other poor in MRPs (white diet). Each diet was administered during a 14-d treatment period. Treatment periods were separated by a 40-d washout period. Three-day assessments of phosphorus balances were performed and fasting blood samples were obtained on the last day of each dietary period. Dietary phosphorus utilization was examined by phosphorus intake in diet and phosphorus output in feces and urine, as measured colorimetrically by the vanadomolybdate procedure. Serum phosphorus, PTH, and total ALP were determined. The results demonstrated a nonsignificant tendency to increased daily phosphorus fecal excretion subsequent to the brown diet consumption compared with the white diet ($P = 0.10$), which led to significant reductions in phosphorus apparent absorption ($P = 0.03$) and fractional absorption of phosphorus ($P = 0.04$). The fractional absorption of phosphorus was reduced by 16% with the high-MRP, brown diet compared with the white diet. Values of apparent phosphorus retention and bioavailability tended to decrease after the high-MRP diet. Serum parameters remained unchanged between diets and were all within normal values. The consumption of a rich-MRP diet by male adolescents had a negative influence on dietary phosphorus absorption, resulting in a nonsignificant trend to a negative phosphorus balance.

A study analyzed the association of FGF-23 with demographic, clinical, dietary, and laboratory factors in 1261 participants (mean age: 64 ± 9 y) from the Health Professionals Follow-up Study (Gutiérrez and others 2011). The Health Professionals Follow-up Study enrolled 51529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40 to 75 y of age in 1986. This cross-sectional study analyzed the associations of demographic, clinical, dietary, and laboratory parameters with plasma FGF-23 levels to identify factors independently associated with higher plasma FGF-23 concentrations in community-dwelling adults with preserved kidney function. The analyses included subjects with traditional and nontraditional risk factors for CVD. Dietary phosphorus was assessed by the self-administered semiquantitative FFQ and the frequency of intake of foods commonly enriched with additives (for example, processed meats, cola beverages). Higher phosphorus intake was associated with higher FGF-23 levels, independently of age, creatinine, and other factors. Higher FGF-23 levels were associated with higher mean serum concentrations of phosphorus, PTH, uric acid, and triglycerides, and lower mean concentrations of HDL. In addition, higher levels of PTH, phosphate, triglycerides, uric acid, and some biomarkers of inflammation were independently associated with higher FGF-23 levels. Adjusted mean daily intakes of dietary phosphorus significantly increased with increasing plasma FGF-23 levels (P for trend 0.03). In contrast, adjusted mean intakes of protein, calcium, and phytate were not associated with different plasma FGF-23 levels. Similarly, there were no differences in the frequency of intake of foods commonly enriched with phosphorus-based food additives (processed meats, colas) across different FGF-23 levels.

The authors conclude that the associations of increased FGF-23 with factors independently linked with excess CVD risk (including obesity, dyslipidemia, smoking, and hypertension) may help delineate reasons for the relationship between excess FGF-23 and adverse outcomes in individuals across the spectrum of kidney function. The authors further note that higher BMI, PTH, serum phosphate, creatinine, and triglycerides remain independent predictors of higher FGF-23 among individuals with mostly preserved kidney function, even after adjusting for key demographic, clinical, and dietary variables. When expressed in "relative units" (RUs), each 500 mg/d increase in phosphorus intake was associated with an FGF-23 concentration that was 3.4 RU/mL higher ($P < 0.02$). For comparison, each increase in serum creatinine concentration of 0.1 mg/dL was associated with an FGF-23 concentration that was 3.4 RU/mL higher ($P < 0.001$). Participants with BMI >30 kg/m^2 had average FGF-23 concentration that was 9.5 RU/mL higher than those with BMI <23 30 kg/m^2.

The author commented that the results contrast with the findings of a recent study that showed no association between FGF-23 and estimated dietary phosphorus intake in nearly 3879 participants of the Chronic Renal Insufficiency Cohort Study with mean eGFR 42.8 ± 13.5 mL/min/1.73 m^2 (Isakova and others 2011). There are a number of potential reasons for this discrepancy. It is possible, for example, that phosphorus intake is more strongly associated with FGF-23 levels in individuals with normal kidney function.

A cross-sectional analysis of 147 healthy women aged 31 to 43 y evaluated how habitual consumption of food with various dietary Ca:P ratios affected serum PTH concentrations and other markers of calcium metabolism in a population of healthy women with generally adequate calcium intake (Kemi and others 2010). The authors hypothesized that low dietary Ca:P ratios have a deleterious impact on calcium metabolism compared with high Ca:P ratios. Fasting blood samples, 3 separate 24-h urinary samples, and 4-d food records were collected and analyzed according to dietary Ca:P ratios.

Forty-four participants had dietary calcium intake below recommended levels (mean intake of 647 mg/d), and none of the participants consumed the suggested dietary Ca:P molar ratio of 1. The overall mean dietary Ca:P ratio was 0.74. Subjects were divided into quartiles based on Ca:P molar ratios, with the highest mean Ca:P molar ratio of 0.92 being in the 4th quartile and lowest mean ratio of 0.56 in the 1st quartile. Serum PTH concentrations differed significantly based on different Ca:P molar ratios. Mean serum PTH concentrations and mean urinary calcium excretion were both significantly higher ($P = 0.021$ and 0.051, respectively) in the 1st quartile (lowest Ca:P molar ratio) than in all other quartiles. After adjusting for covariates, urinary phosphorus excretion was significantly greater in the 1st quartile than in the other quartiles. Mean serum calcium levels were greatest in the 4th quartile (greatest mean Ca:P ratio).

The associations of the different Ca:P molar ratios on calcium metabolism were different in each quartile. The 1st quartile with Ca:P molar ratio ≤0.50 differed significantly from the 2nd quartile (Ca:P molar ratio, 0.51 to 0.57), 3rd quartile (Ca:P molar ratio, 0.58 to 0.64), and 4th quartile(Ca:P molar ratio, ≥0.65) by interfering with calcium metabolism. The greatest significant increase in serum PTH concentrations and urinary calcium concentrations were observed in subjects with the lowest Ca:P intake ratios. The authors concluded that the results suggest that habitual diets with low Ca:P molar ratios may interfere with homoeostasis of calcium metabolism and increase bone resorption, as indicated by higher serum PTH and urinary calcium concentrations.

Obeid and others (2010) conducted a series of small studies to evaluate the impact of phosphorus content in meals on hepatic adenosine triphosphate synthesis and on satiation. Fifty-three healthy male and female subjects (mean age: 20.7 to 26.6 y) participated. The studies investigated the effect of increased phosphorus content of a preload solution on subsequent food intake. The studies examined the effect of water, sucrose (50 g), fructose (40 g fructose plus 10 g glucose), or glucose (50 g) preloads each with or without the addition of 500 mg of phosphorus (mixture of potassium and sodium phosphate). Subjects maintained their regular dietary and physical activity habits throughout the course of the study. In each experiment, 2 chilled preloads (with or without added phosphorus) were administered in a blinded, randomized order so as to control for the order-of-treatment effect. A total of 400 mL of the preload solutions were administered to subjects. Each subject presented for 2 study days separated by a minimum of 1 wk. In all experiments, the preloads with added phosphorus were associated with significant reductions in energy intake at subsequent meals. The phosphorus content of the different preloads was found to be inversely related to the energy intake at a subsequent meal, although the exact mechanism behind such effects was not studied. The author concluded that added loads of phosphorus reduced subsequent food intake, although the exact mechanism was not known.

Fifteen volunteers participated in a randomized, controlled, double-blind crossover study that evaluated the absorption of calcium from 5 types of semiskimmed milk: standard milk (control milk); milk enriched with calcium from milk solids (MSS), and tricalcium phosphate (TCP) (MSS milk); milk enriched with calcium from concentrated milk; milk with added fructooligosaccharides (FOSs) (FOS milk); and milk with added caseinophosphopeptides (CPPs) (CPP milk) (López-Huertas and others 2006). All the milks were labeled with ^{42}Ca as calcium chloride ($CaCl_2$). The MSS milk was also labeled with ^{44}Ca as TCP. The quantity of calcium in each drink was kept the same by varying the volume given. Calcium absorption did not differ significantly between the control milk and the calcium-fortified milks (MSS and concentrated milk) or the FOS and CPP milks. However, calcium absorption from the TCP added to the MSS milk was significantly higher than that from the control milk ($27.5 \pm 7.6\%$ and $24.5 \pm 7.3\%$, respectively; $P = 0.003$). The authors concluded that absorption of added calcium as TCP was greater than that of calcium from the control milk, but the addition of FOSs or CPPs did not significantly increase calcium absorption.

An observational trial evaluated 191 Roman Catholic nuns aged 48.7 ± 7.0 y with a full metabolic balance regimen and controlled, chemically analyzed diets (Heaney 2000). The study evaluated whether variations in phosphorus and protein intakes were associated with variations in calcium absorption. Metabolic balance and absorption studies were performed over approximately 5-y intervals over 32 y. Calcium and phosphate intake and elimination were measured during the metabolic balance studies. The results indicated that the observed protein intakes varied by the subjects. Protein intake ranged from 0.41 to 1.96 g/kg, phosphorus intake from 0.45 to 2.45 g/d, and relative absorption of calcium from 0.33 to 2.25 times that predicted for the respective calcium intake. There was no relationship between the relative absorption of calcium and either phosphorus or protein intake. In multivariate models, age, body weight, and estrogen status were highly significant predictors of relative absorption of calcium. However, protein and phosphorus intakes made no contribution to the model. In conclusion, there was no relationship between calcium absorption efficiency and either protein or phosphorus intake.

Brot and others (1999) evaluated the relationships between serum vitamin D metabolites, bone mass, and dietary calcium and phosphorus in an observational cohort of healthy Danish perimenopausal women. The study evaluated 510 healthy women, aged 45 to 58 y, not using HRT and who had amenorrhea for 3 to 24 mo. Calcium and phosphorus intake were assessed using 4- or 7-d dietary records. The analyses revealed that there were no relationships between levels of PTH, serum ionized calcium and phosphate, and serum vitamin D metabolites. There was a high correlation between calcium and phosphorus intake ($r = 0.866$; $P < 0.0005$). However, dietary phosphorus was not related to serum 25-(OH)D, serum $1,25(OH)_2D$, or PTH. The calculated calcium to phosphorus ratio in the diet was negatively related to levels of $1,25(OH)_2D$ ($P = 0.04$) but did not correlate with serum PTH or plasma phosphorus or calcium levels. A higher dietary calcium:phosphorus ratio was reported to be associated with higher bone mass.

All the studies that evaluated the association of dietary phosphorus with regulatory hormones or other physiological effects were short-term, small studies that were either cross-sectional analyses of observational cohorts or small prospective studies that enrolled healthy adult individuals.

The quality of evidence is considered high for 3 studies (López-Huertas and others 2006; Obeid and others 2010; Delgado-Andrade and others 2011) and low for 5 studies (Brot and others 1999; Heaney 2000; Kemi and others 2009; Gutiérrez and others 2011; Ito and others 2011) based on the design of studies as defined in Appendix C. The results from 8 studies that evaluated the physiological effects associated with dietary phosphorus revealed the following:

- In healthy individuals, greater intake of dietary phosphates was associated with increased serum PTH and FGF-23 concentrations (Kemi and others 2010; Gutiérrez and others 2011).

Increases in FGF-23 levels were noted to be independent of age and serum creatinine while serum BMI, PTH, and serum phosphorus were noted to be independent predictors of increases in FGF-23.

- Three studies evaluated the effects of consuming meals with different Ca:P ratios. Two studies demonstrated that in healthy individuals, there was no relationship between most meals with different Ca:P ratio and changes in serum PTH levels. One study reported that increased serum PTH levels were only associated with consuming diets with the lowest dietary Ca:P molar ratios (Kemi and others 2010). In this study, molar ratios in meals ranged from 0.22 to 0.92, and no participants consumed meals with the targeted Ca:P molar ratio of 1; all meals had Ca:P ratios <1. A cross–sectional study detected no relationship between the Ca:P ratio in diets with serum PTH levels or with plasma phosphorus or calcium levels in healthy perimenopausal women. (Otten and others 2006). One study was unable to identify a relationship between calcium absorption efficiency and either protein or phosphorus intake (Heaney 2000).
- The method of food preparation was reported to be associated with differences in phosphate absorption (Delgado-Andrade and others 2011). Diets rich in MRPs resulted in significantly reduced fractional absorption of phosphorus compared with normal diets consumed by male adolescents. However, there were no differences in serum phosphorus, calcium, or PTH levels between the subjects consuming the different diets.
- Calcium absorption was significantly increased after consumption of milk enriched with TCP compared with milk that was either not enriched or contained different nutrient compounds (López-Huertas and others 2006).

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included, variously, the limited ability of the implementation of short-term dietary alterations to draw conclusions about the effects of habitual diets, and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Association of phosphorus load with regulatory hormones and other physiological outcomes. This section summarizes 8 studies that evaluated the effects of consuming additional amounts of phosphates either as supplements to diets or administered in greater than currently recommended amounts, as food with high amounts of dietary phosphorus, on regulatory hormones and physiological outcomes. A description of the diets used in the studies is provided in Table 7.

A double-blind, placebo-controlled, parallel-group study evaluated the influence of a high phosphorus intake in combination with different amounts of calcium intake on phosphorus, calcium, magnesium, and iron metabolism and on plasma FGF-23 concentrations (Trautvetter and others 2016). The study enrolled 66 healthy adults (33 men, 33 women) and evaluated the results from 62 individuals; 4 subjects were excluded from the study for personal reasons. Mean ages in the 3 treatment groups ranged from 28 ± 6 y to 29 ± 8 y. At the beginning of the study, nutritional habits and diets were recorded for 7 d, and 24-h urine and fasting blood samples were collected to establish baseline profiles. Subjects were then blindly randomized to 3 intervention groups so that there were no differences in age, BMI, or plasma 25(OH)D levels between the 3 groups. Each group received 1000 mg of phosphate each day in the form of monosodium phosphate (NaH_2PO_4) combined with 0, 500, or 1000 mg calcium carbonate ($CaCO_3$) per day (designated as P1000/Ca0, P1000/Ca500, P1000/Ca1000). During the 1st 2 wk, all subjects consumed placebo products, and during the next 8 wk, subjects consumed their respective calcium and phosphate supplement intervention. Blood, urine, and fecal samples were collected before, during, and after the treatment periods. The results of the physiological effects of the different supplemented diets were reported as changes from baseline after 4 and 8 wk. The results demonstrated that the additional intake of 1000 mg phosphorus per day did not influence fasting plasma phosphate concentrations of healthy adults after 8 wk of intervention, independent of calcium intake. There were no differences in the changes in plasma PTH concentrations between the 3 diets. Plasma $1,25(OH)_2D$ increased in all intervention groups after 8 wk of supplementation compared with placebo, but significantly increased in only the P1000/Ca0 group. There was significant variability between subjects in changes in the plasma FGF-23 levels after 4 and 8 wk, particularly in subjects who received the 0- and 500-mg calcium supplements. Five subjects had greater FGF-23 concentrations than other subjects in at least one study period. However, these subjects had normal calcium and phosphorus levels and did not suffer from CKD. After adjustments, FGF-23 concentrations were significantly greater after 4 wk compared with 8 wk of intervention in all groups (P1000/Ca0, $P = 0.023$; P1000/Ca500, $P = 0.005$; P1000/Ca1000, $P = 0.001$). FGF-23 appeared to increase transiently after phosphorus supplementation and decreased after 8 wk of supplementation. The results of the remaining 56 subjects were similar in the 3 intervention groups. The FGF-23 concentrations increased on average by 17% after 4 wk of supplementation compared to placebo (only significant for the 1000-mg calcium group) and decreased by 33% after 8 wk compared to 4 wk of supplementation. Plasma magnesium concentrations did not change after any intervention; however, renal magnesium excretions were statistically significantly decreased after 4 and 8 wk after only the phosphorus supplementation but without the calcium supplementation (P1000/Ca0). Renal calcium excretion significantly decreased after 4 wk ($P = 0.001$) and 8 wk ($P = 0.029$) of P1000/Ca0 intervention compared to placebo. Fecal calcium concentrations were significantly increased after 8-wk intervention compared to placebo in the P1000/Ca500 ($P \leq 0.001$) and P1000/Ca1000 ($P \leq 0.001$) groups.

The authors noted that short-term exposure to an additional intake of 1000 mg phosphorus did not influence fasting plasma phosphate concentrations of healthy adults, independent of calcium intake. The authors concluded that high phosphorus intake without adequate calcium supplementation seems to have a negative impact on calcium metabolism and a well-balanced Ca:P ratio is an important prerequisite for a normal metabolism of calcium.

An open-label, crossover study evaluated the effects of high- and low-phosphate and calcium diets on serum FGF-23, PTH, and vitamin D levels and urinary phosphorus excretion in 10 healthy subjects taking high- and low-phosphate and calcium diets (Vervloet and others 2011). Diets were administered during 2 study periods of 3 d each, separated by a 1-wk interval. A dietician prescribed the dietary intervention meals for each study period. Phosphorus and calcium contents of the diets were designed by the dietician. During the 1st study period, subjects consumed a low-phosphate (850 mg) and calcium (280 mg) diet, and, during the 2nd period, a high-phosphate (2880 mg) and calcium

Table 7–Summary of clinical studies evaluating phosphorus load and physiological outcomes

Study reference	Study population	Methods to determine dietary intake	Duration
Trautvetter and others (2016)	62 healthy individuals; 33 males, 33 females (mean ages: 28 ± 6 to 29 ± 8 y)	Each group received 1000 mg of monosodium phosphate (NaH_2PO_4) supplements each day and 0, 500, or 1000 mg calcium carbonate ($CaCO_3$) supplements per day for 8 wk.	10 wk
Vervloet and others (2011)	10 healthy medical students	First study period (1 wk): low dietary phosphate (850 mg/d) and calcium (280 mg/d) diet. Second study period (1 wk): high dietary phosphate (2880 mg/d) and calcium (1700 mg/d) diet.	2 wk
Kemi and others (2008)	12 healthy females (mean age: 24 y)	The meals on study days consisted of phosphorus 1850 mg/d and calcium 480 mg/d. The study included a control day, representing low calcium (480 mg) and higher phosphorus 1850-mg intake (Ca:P ratio of 0.26), a 600-mg calcium day (adequate calcium), representing adequate calcium (1080 mg) and high phosphorus (1850 mg) intake (Ca:P ratio 0.58), and a 1200-mg calcium day (high calcium), representing high calcium (1680 mg) and phosphorus (1850 mg) intake (Ca:P ratio of 0.91). The main P sources were meat products (32%), grain products (19%), milk products (17%), and eggs (7%). Standardized meals and 4-d food records were maintained on days between each study session.	1 mo
Karp and others (2013)	16 healthy women (20 to 30 y of age)	Phosphorus from 3 diets: meat sessions (ham and beef steak), cheese (fermented cheese), and whole grain (oatmeal and nonfermented rye bread).	1 d
Antoniucci and others (2006)	13 healthy males (28 to 43 y of age)	A constant diet provided 500 mg of phosphorus per day, which was supplemented to achieve 3 different quantities of phosphorus intake over 9 d: (1) 1500 mg/d; (2) supplemented to 2300 mg/d; and (3) restricted to 625 mg/d. Total oral phosphorus intake was achieved by supplementing wholefood diet with a solution of neutral sodium and potassium phosphate (4:1 mixture of Na_2HPO_4/K_2HPO_4 and NaH_2PO_4/KH_2PO_4, 31 mg phosphorus, 0.9 mEq sodium, and 0.9 mEq potassium per 5 mL). The basic diet provided, by calculation, 2000 kcal/d, 9% as protein, 34% as fat, and 57% as carbohydrate.	4 wk
Nishida and others (2006)	8 healthy males (20 to 34 y of age)	Lunch consisted of either 400, 800, or 1200 mg phosphorus.	1 d
Burnett and others (2006)	66 healthy subjects (28 males, 38 females) (Age: phosphate-depleted group 28 ± 8 y; phosphate-loaded group 26 ± 7 y)	Phosphate-depleted group received 2.2 g of aluminum and magnesium hydroxide 4 times a day with meals to decrease absorption of dietary phosphate. Phosphate-loaded group received phosphate supplements (either Neutra-Phos or Phos-NaK) 4 times a day with meals such that the total daily phosphate intake was 2500 mg (500 mg from the diet and 2000 mg from the supplements).	9 d
Portale and others (1996)	16 healthy men; 7 elderly (mean age: 71 y); 9 young men (mean age: 29 y)	A constant whole food diet provided 550 mg phosphorus and 170 mg calcium for 26 d. First 9 d, phosphorus was 1500 mg/d by adding 950 mg phosphorus supplement. Phosphorus increased next 8 d to 2300 mg/d by administering 1750 mg/d phosphorus. Phosphorus decreased the next 8 d to 625 mg/d by adding 75 mg/d supplemental phosphorus.	26 d

Ca:P, calcium to phosphorus ratio; P, phosphorus.

(1700 mg) diet. Simultaneous high or low calcium and phosphate were given to prevent a phosphate-induced increase in PTH. Ten subjects received diets that were low or high in phosphate and calcium contents for 36 h each, with a 1-wk interval during which time subjects adhered to their usual diet. Serum phosphate, calcium, vitamin D metabolites, PTH, and FGF-23 levels were measured several times daily, and phosphate, calcium, and creatinine excretion were measured during the 24-h urine collection periods on all study days.

The 2 dietary interventions led to significant changes in 24-h urinary urea content confirming that there was reasonable separation in the levels of protein intake. Creatinine clearance decreased during phosphate/calcium restriction and increased during phosphate/calcium-enriched meals. Serum phosphorus concentrations did not change during dietary phosphate/calcium restriction compared with baseline (1.09 ± 0.12 mg/dL compared with 1.07 ± 0.14 mg/dL; $P = 0.22$) but were significantly increased during high dietary phosphate/calcium intake (1.11 ± 0.13 mg/dL compared with 1.25 ± 0.15 mg/dL; $P = 0.0001$). There were no significant changes from baseline in serum calcium concentrations with either diet. PTH levels were unchanged after phosphate-/calcium-restricted meals (mean PTH 5.7 ± 2.6 pmol/L on regular diet, followed by mean PTH 5.4 ± 2.2 pmol/L (not significant) on the subsequent day with a phosphate-/calcium-restricted diet). However, phosphate-/calcium-enriched meals led to a significant decrease in serum PTH levels from 5.2 ± 2.8 to 4.3 ± 1.6 pmol ($P = 0.008$ after correcting for serum calcium and phosphorus). There was a significant inverse correlation between PTH and phosphate content of meals ($P = 0.006$). There were no changes in the levels of vitamin D metabolic products during the entire study. FGF-23 serum levels increased significantly ($P = 0.003$) during high dietary phosphate/calcium intake and were only slightly reduced during the phosphate-/calcium-restricted diet. Urinary phosphate excretion tended to decrease ($P = 0.09$) during phosphate/calcium restriction and significantly increased ($P = 0.005$) during high dietary phosphate/calcium intake. There were no changes in the levels of vitamin D metabolic products during the entire study. However, a multivariate analysis revealed a significant and independent effect of phosphate-/calcium-enriched meals on the levels of $1,25(OH)_2D$ even after correcting for PTH and FGF-23, demonstrating lower $1,25(OH)_2D$ levels with phosphate-/calcium-enriched meals.

The authors suggested that the results from this study combined with data from other studies indicate that phosphate loading results in a prompt response of PTH, causing very early phosphaturia. However, within 8 to 16 h of continued high phosphate intake, FGF-23 increases and takes over the phosphaturic effects of PTH. The authors concluded that decreases of serum PTH concentrations during phosphate-enriched meals may have been associated with a simultaneous increase in calcium intake and, therefore, changes in serum PTH levels cannot explain the change in phosphaturia.

A randomized, controlled study evaluated the dose–response effects of calcium intake on calcium and bone metabolism with a greater than recommended dietary phosphorus intake (Kemi and others 2008). Each of the 12 healthy female subjects, aged 21 to 40 y (mean 24 y), attended three 24-h study sessions over a 1-mo study period, separated by at least 1 wk between each session. Subjects received supplemented calcium doses of 0 (control day), 600, or 1200 mg, and each subject served as her own control. The meals provided 480 mg calcium and 1850 mg phosphorus on each study day. The study design included the following:

- A control day, where subjects received low calcium (480 mg) and 2.5-fold higher phosphorus (1850 mg) intake than the current RDA (Ca:P ratio of 0.26)
- A 600 mg calcium day (adequate calcium), representing adequate calcium (1080 mg) and high phosphorus (1850 mg) intake (Ca:P ratio 0.58)
- A 1200-mg calcium day, representing high calcium (1680 mg) and phosphorus (1850 mg) intake (Ca:P ratio of 0.91)

The order of the study sessions was randomized. Standardized meals and 4-d food records were maintained on days between study sessions. Blood samples were obtained in the morning after a 12-h overnight fast and then at 4 additional times during the day. A 24-h urine sample was collected during each session. The results demonstrated that with increasing doses of calcium, serum PTH concentration decreased ($P < 0.001$), serum ionized calcium concentration increased ($P < 0.001$), and serum BALP did not change. When phosphorus intake was greater than the current recommendations, serum PTH concentration and bone resorption decreased. The authors noted that when phosphorus intake was above the dietary guidelines (700 mg/d), oral calcium intake decreases serum PTH concentration and bone resorption, which both have been induced by increased phosphorus intake. The authors noted that the dietary Ca:P ratio was important, and the results support the hypothesis that high calcium intake may not be sufficient to overcome adverse effects of high dietary phosphorus intake on calcium metabolism within 24 h.

Kemi and others (2006) studied the short-term effects of 4 different oral phosphate doses on calcium and bone metabolism in 14 healthy women. Subjects were randomized to 4 study days during a 1-mo period with 1 wk between sessions. Each subject served as her own control. Subjects were given 0 (placebo), 250, 750, or 1500 mg phosphorus as a mixture of disodium phosphate and trisodium phosphate, commonly used phosphate additives in the food industry. Phosphorus was mixed with orange juice and served in 3 equal separate doses with food during the day. Meals were identical for all subjects on each study day. Blood samples were collected at 08:00 after an overnight fast on the study day, and at 12:00, 14:00, 16:00, 18:00, and 08:00 the following morning. Urine samples were collected for 24 h starting at 08:00 on the study day. Serum phosphate, serum, calcium, urinary phosphate, urinary calcium, and urinary creatinine were analyzed by spectrophotometry. There was a significant dose–response relationship in serum phosphorus concentration in relation to phosphorus doses ($P = 0.0005$, ANOVA). This increase was most profound after the 2 highest doses. Serum calcium concentrations decreased in response to phosphorus intake ($P = 0.0005$, ANOVA). Serum PTH concentration increased in a dose-dependent manner in response to phosphorus intake ($P = 0.0005$, ANOVA). Urinary phosphorus excretion increased in a dose-dependent manner with increasing phosphorus doses ($P = 0.0005$, ANOVA). The increase in serum PTH exposure positively correlated with the morning fasting serum $1,25(OH)_2D$ concentration ($r = 0.57$; $P = 0.035$). Load of phosphorus intake was inversely associated with serum concentrations of biomarkers of bone metabolism. There was a significant decline in serum (BALP) activity after the 750 and 1500 mg phosphorus doses.

The acute effects of dietary phosphorus from 3 different food sources and a phosphate supplement on calcium and bone metabolism were investigated (Karp and others 2007). Sixteen healthy women, aged 20 to 30 y, from Finland, were randomized to 5 controlled, 24-h study sessions, at 7-d intervals, each subject serving as her own control. During the control session, phosphorus intake was 500 mg; however, during the other 4 sessions, phosphorus intake was approximately 1500 mg/d, of which 1000 mg was obtained from meat, cheese, whole grains, or a phosphate supplement. The main phosphorus sources at meat sessions were ham and beef steak, both prepared without phosphate additives, at cheese sessions were fermented cheese, and at whole-grain session were oatmeal porridge and nonfermented rye bread. The foods served were exactly the same during the phosphorus sessions and the control session; only phosphorus sources varied. Blood samples were collected before meals, at 08:00 and 14:00, and immediately after meals. The 24-h urine samples were collected during the study sessions.

Urinary phosphate excretion was significantly higher in all phosphate sessions than in the control session ($P = 0.001$ to 0.0001). Meat increased urinary phosphate excretion more than grain ($P = 0.003$) or cheese ($P = 0.005$). The phosphate supplement also increased urinary phosphate excretion more than grain ($P = 0.001$) or cheese ($P = 0.027$). The different amounts of phosphates in foods affected the serum and urinary calcium excretion. During the phosphate-supplemented session, serum calcium concentration was significantly lower than in the control session ($P = 0.027$), while meals with whole grains ($P = 0.682$) and meat ($P = 0.282$) had no effect on serum calcium concentration relative to the control session. During the meat session, the calcium excretion was significantly greater than in the phosphate supplement session ($P = 0.003$). Serum PTH levels were not changed during meat or grain meals. Only the phosphate supplement increased serum PTH concentrations compared with the control session ($P = 0.031$). Cheese decreased serum PTH concentrations the most ($P = 0.0001$). Serum creatinine concentrations were higher during the meat sessions than any of the other sessions ($P = 0.0001$) because meat has a high creatine content. The authors concluded that the effects of high phosphorus intake appeared to depend on the source of phosphorus consumed. Based on serum phosphorus and urinary phosphate excretion, phosphorus from meat and supplements appeared to be absorbed better than phosphorus from whole grains. The authors stated that phosphate compounds commonly used by the food industry seem to be absorbed well and increase serum PTH, while phosphorus from meat or whole grains did not appear to affect serum PTH concentrations.

An interventional study evaluated whether serum FGF-23 concentration is regulated by dietary phosphorus and thereby mediates the physiological response of serum $1,25(OH)_2D$ to changes in dietary phosphorus (Antoniucci and others 2006). The study enrolled 13 healthy male volunteers, aged 28 to 43 y, who were administered 3 different phosphate diets during a 4-wk period as inpatients. Subjects consumed a constant diet that provided 500 mg of phosphorus per day, which was supplemented to achieve 3 different quantities of phosphorus intake over 9 d: (1) control = 1500 mg/d; (2) supplemented = 2300 mg/d; and (3) restricted =

625 mg/d. The intakes of magnesium and calcium were held constant at 350 and 850 mg/d by supplementing the diet with orally administered magnesium sulfate and calcium carbonate, respectively. The results demonstrated that dietary phosphorus intake had significant effects on serum FGF-23, $1,25(OH)_2D$, and on serum iPTH concentrations. Serum $1,25(OH)_2D$ concentrations were significantly greater during phosphorus restriction (40 ± 16 pg/mL) and lowest with phosphorus supplementation (29 ± 10 pg/mL) (both changes: $P < 0.001$). Serum FGF-23 concentrations increased slightly (not statistically significant) when dietary phosphorus was supplemented to 2300 mg/d but were statistically significantly decreased ($P < 0.001$) when dietary phosphorus was restricted to 625 mg/d. Serum iPTH was significantly decreased ($P = 0.003$) when phosphorus intake was restricted and was significantly increased ($P < 0.001$) when dietary phosphorus was supplemented. Urinary phosphorus excretion increased by 78% ($P < 0.001$) with supplemented dietary phosphorus and decreased by 71% ($P < 0.001$) with restricted dietary phosphorus. Urinary calcium excretion varied indirectly with dietary phosphorus intake ($P < 0.001$) in that the higher dietary phosphorus resulted in lower urinary calcium excretion. In contrast, serum calcium concentrations remained constant throughout the 3 study periods. The authors concluded that, in healthy men, manipulation of dietary phosphorus within the commonly observed dietary range of intakes regulates serum FGF-23 concentrations and that the data suggest that regulation of $1,25(OH)_2D$ production by dietary phosphorus is mediated, at least in part, by changes in circulating FGF-23. When subjects ingested a phosphorus-supplemented diet (2300 mg/d), serum FGF-23 concentrations were 57% higher than those observed when dietary phosphorus was low-normal (625 mg/d). Similarly, when phosphorus intake was 1500 mg/d, serum FGF-23 concentrations were 32% higher than those observed on the low-normal phosphorus intake.

A randomized, double-blind, crossover study evaluated the acute effects of oral phosphorus loading on serum FGF-23 levels in 8 healthy male volunteers (mean: 21.4 y) (Nishida and others 2006). The authors hypothesized that FGF-23 may, in part, mediate the rapid regulation of phosphorus homeostasis. Subjects were alternately served 1 of 3 test meals containing different amounts of phosphorus: 400, 800, and 1200 mg phosphorus for lunch at noon. Postprandial changes in serum levels of $1,25(OH)_2D$, iPTH, and urinary excretion of phosphorus and calcium 8-h after phosphorus loading were evaluated. Serum phosphorus concentrations after the test meals increased over 8 h as the intake of phosphorus increased. The cumulative urinary phosphorus excretion was significantly increased in response to phosphorus loading. Urinary phosphorus excretion gradually increased until 6 h after ingestion of the 400-mg meal, while the excretion after 800- and 1200-mg meals increased significantly within 1 h compared with that after the 400-mg meal. The fractional renal tubular reabsorption rate of phosphorus was decreased by phosphorus loading; this decrease was dose dependent. There were no significant changes in serum calcium or $1,25(OH)_2D$ levels as the intake of phosphorus increased. There were no significant changes in urinary calcium excretion in response to phosphorus loading. Serum iPTH levels were significantly increased at 1, 2, and 4 h after the 800- and 1200-mg meals as compared with those after the 400-mg meal. The serum iPTH levels were significantly associated with both serum phosphorus levels and renal phosphorus reabsorption rate ($P < 0.05$). Serum intact FGF-23 levels were decreased or not changed up to 6 h after all diets, but modestly increased at 8 h after the highest phosphorus loading. A statistically significant negative association was detected between intact FGF-23 and serum phosphorus levels ($P < 0.05$), whereas a positive association was observed between intact FGF-23 and renal phosphorus reabsorption rate. The results indicated that dietary phosphorus intake acutely decreased renal phosphate reabsorption and increased serum PTH levels within 1 h after phosphorus loading. The authors suggest that FGF-23 may not be involved in the rapid regulation of phosphorus homeostasis but FGF-23 may act as a phosphaturic factor.

An open-label randomized trial was designed to evaluate the physiological role of dietary phosphate on the regulation of FGF-23 in humans (refer to Section "Total dietary phosphorus and serum phosphorus concentration" for description of study) (Burnett and others 2006). FGF-23 was measured using 2 different immunometric assays. Serum PTH, 25-(OH) D, and $1.25\text{-}(OH)_2D$ were measured and both serum and urine phosphates were measured. The mean 24-h urinary phosphate excretion was similar at baseline in both groups, decreased from 500 ± 192 (16 ± 6 mmol) to 79 ± 85 mg (3 ± 3 mmol) with dietary phosphate depletion ($P < 0.01$) and increased from 447 ± 155 (14 ± 5 mmol) to 1044 ± 318 mg (34 ± 10 mmol) with phosphorus loading ($P < 0.01$). The mean fractional excretion of phosphate (F_ePO_4, reference range: 0% to 20%) decreased from 9 ± 4% to 2 ± 3% with dietary phosphate depletion ($P < 0.01$) and increased from 10 ± 6% to 16 ± 4% with phosphate loading ($P < 0.01$). Mean 24-h urinary calcium excretion was similar in both groups at baseline and increased from 170 ± 62 (4.2 ± 1.5 mmol) to 210 ± 87 mg (5.2 ± 2.2 mmol) with phosphate depletion ($P < 0.01$) and decreased from 174 ± 102 (4.3 ± 2.5 mmol) to 93 ± 73 mg (2.3 ± 1.8 mmol) with loading ($P < 0.01$). Mean serum $1,25(OH)_2D$ levels increased from 49 ± 22 (118 ± 53 pM) to 62 ± 29 pg/mL (149 ± 70 pM) with dietary phosphate depletion ($P < 0.01$) but did not change with phosphate loading ($P = 0.16$). Serum PTH levels did not change with phosphate depletion ($P = 0.81$) but increased from 35 ± 14 ng/L to 43 ± 15 ng/L with loading ($P < 0.01$). Blood calcium levels were stable and did not change with both interventions.

The results demonstrated that under acute conditions, dietary phosphate deprivation significantly reduced phosphate excretion, iron phosphate (F_ePO_4), and serum phosphate levels, and increased urinary calcium excretion and serum $1,25(OH)_2D$ levels. Increasing exposure to phosphate significantly increased urinary phosphate excretion, F_ePO_4, and serum PTH, decreased urinary calcium excretion, and did not change serum $1,25(OH)_2D$ levels.

A prospective study evaluated the effects of aging on the physiological regulation of the serum concentration of $1,25(OH)_2D$ by inorganic phosphorus (Portale and others 1996). A prospective study enrolled 16 healthy men with GFR > 70 mL/min: 7 elderly (mean age: 71 y) and 9 young (mean age: 29 y). A constant whole food diet provided 550 mg phosphorus, 170 mg calcium, 85 mg magnesium, and 80 mEq sodium per 70 kg body weight for 26 d. The intakes of calcium and magnesium were maintained with calcium carbonate and magnesium sulfate supplements. The intake of phosphorus was changed by altering the amount of phosphorus administered orally as a solution of neutral sodium and potassium phosphate. For the 1st 9 d, the intake of phosphorus was 1500 mg/d, achieved by administering 950 mg/d supplemental phosphorus. For the next 8 d, phosphorus intake was increased to 2300 mg/d by administering 1750 mg/d supplemental phosphorus; for the subsequent final 8 d, phosphorus intake was decreased to 625 mg/d by administering 75 mg/d supplemental phosphorus.

When dietary phosphorus was supplemented from 1500 to 2300 mg/d, the serum concentration of $1,25(OH)_2D$ in the

elderly men did not change significantly, whereas, in the young men, it decreased by 16% ($P < 0.05$). When dietary phosphorus was subsequently restricted to 625 mg/d, the serum concentration of $1,25(OH)_2D$ increased in each subject; the increase was statistically significant after 2 d in the young and after 4 d in the elderly men. After 8 d of phosphorus restriction, serum concentration of $1,25(OH)_2D$ increased in elderly men by 47% and in the young men by 46%. These increases were noted in all subjects ($P < 0.01$). Fasting and 24-h mean serum calcium levels were significantly lower in elderly men in both high and low dietary phosphorus. Serum PTH levels were greater in elderly men than young men. Serum $1,25(OH)_2D$ decreased linearly with increasing mean 24-h serum phosphate levels. This relationship was shifted to the left in elderly men. There was no significant relationship between age and serum phosphorus concentration. There was no relationship between serum PTH and serum $1,25(OH)_2D$. Urinary phosphorus and calcium excretion was lower in the elderly men than in young men. When dietary phosphorus was supplemented and then restricted in the elderly men and the young men, both the 24-h urinary excretion of phosphorus and the FEP increased and then decreased, respectively, rapidly and substantially. Neither the magnitude nor the time course of changes induced in urinary phosphorus excretion differed between the groups of men. Urinary excretion of calcium decreased when phosphorus was supplemented; increased progressively when phosphorus was restricted; and, after 5 d, had approximately doubled in both groups of men. Neither the magnitude nor the time course of changes in calcium excretion differed between the 2 groups.

In summary, 8 studies evaluated the physiological effects associated with consumption of additional amounts of phosphorus either by meals supplemented with phosphorus or by consuming additional food with high amounts of dietary phosphorus. Based on the design of the studies as defined in Appendix C, the quality of evidence is considered high for 4 studies and moderate for 4 studies. The results of the studies revealed the following:

- Variable effects of phosphate-supplemented diets on serum PTH levels. Greater intake of phosphorus was associated with increased serum PTH and FGF-23 concentrations in healthy individuals (Nishida and others 2006; Gutiérrez and others 2010; Kemi and others 2010). Increases in FGF-23 levels were determined to be independent of age and serum creatinine while BMI, PTH, and serum phosphate were shown to be independent predictors of increases in FGF-23. However, one study determined that PTH levels were unchanged after phosphate-/calcium-restricted meals, while phosphate-/calcium-enriched meals led to a significant decrease of PTH levels (Vervloet and others 2011). These data suggest that the effects of different quantities of phosphate intake on serum PTH levels are influenced by the amounts of calcium ingested in healthy individuals. Changes in PTH are affected by both phosphate and calcium, and results of the studies suggest that changes in PTH are influenced by changes in the dietary Ca:P ratio.
- Serum FGF-23 concentrations were increased after administration of phosphate-supplemented diets in healthy individuals (Antoniucci and others 2006; Gutiérrez and others 2010).
- A study noted no changes in plasma PTH concentrations in a short-term study that administered 3 diets with different Ca:P ratios (P1000, P1000/Ca500, and P1000/Ca1000) in healthy individuals (Trautvetter and others 2016). After adjusting for covariates, FGF-23 concentrations were significantly greater after 4 wk compared with 8 wk of consuming the 3 diets. FGF-23 levels appeared to increase transiently after phosphorus supplementation and decreased after 8 wk of supplementation. Both renal and fecal calcium excretion increased after consuming the 3 diets.
- One study reported that increased serum PTH levels were only associated with the lowest dietary Ca:P molar ratios (Kemi and others 2010). In this study, molar ratios in meals ranged from 0.22 to 0.92, and no participants consumed meals with a Ca:P molar ratio of 1.
- Increases in urinary phosphorus excretion paralleled increases in phosphorus intake, and were similar in young and elderly healthy individuals (Portale and others 1996). Urinary excretion of calcium decreased when phosphorus was supplemented and increased progressively when phosphorus was restricted, with no differences due to age.
- Dietary phosphorus from various foods and foods supplemented with phosphate affected calcium and phosphate serum levels and urinary excretion (Karp and others 2007). Urinary phosphate excretion was increased after consuming diets that contained dietary phosphates. Urinary phosphate and calcium excretion was greater after consuming meat products than other foods. However, serum PTH was only decreased after consuming cheese and was not affected by other foods containing phosphates. Serum PTH was decreased after supplementing foods with additional phosphates.
- The method of food preparation was associated with differences in phosphate absorption (Delgado-Andrade and others 2011). Diets rich in MRPs resulted in significantly reduced fractional absorption of phosphorus compared with normal diets consumed by male adolescents. However, there were no differences in serum phosphorus, calcium, or PTH levels between groups receiving the 2 diets.
- Changes in dietary phosphorus were associated with changes in serum concentrations of vitamin D metabolites. Serum concentrations of $1,25(OH)_2D$ were greater during phosphorus restriction and were reduced after phosphorus supplementation (Antoniucci and others 2006). The effects of phosphorus supplementation were different in elderly men; serum $1,25(OH)_2D$ concentrations in the elderly men were not significantly changed after phosphorus intake was increased but concentrations were increased after phosphorus restriction (Portale and others 1996).

Overall, the results from the 8 studies that evaluated the physiological outcomes associated with consumption of supplemented or additional amounts of phosphorus in healthy individuals noted that changes in serum FGF-23, PTH, vitamin D levels, and serum $1,25(OH)_2D$ concentrations were highly variable and were not always associated with increases in phosphorus intake. Changes in serum FGF-23 concentrations appeared to be associated with serum phosphorus concentrations to a greater degree than with the quantity of dietary phosphorus. When serum phosphorus concentrations were increased, FGF-23 concentrations were also increased, but when dietary phosphorus was increased, FGF-23 levels were not consistently increased. Serum PTH levels were more directly associated with changes in dietary Ca:P ratios than with changes in dietary or supplemented phosphorus.

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included the limited ability of the outcomes of phosphorus-intake manipulation through the administration of phosphorus

supplements (or the implementation of other short-term dietary alterations) to draw conclusions about the effects of habitual diets; and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Dietary phosphorus and clinical outcomes

Only 2 primary research publications focused on data potentially specific to a direct association between a phosphorus food additive and a clinical outcome. These publications report a positive association between consumption of cola beverages and bone fracture. The publications present evidence of low quality according to the rating scale employed in the white paper and are summarized in Section "Food–additive phosphate and clinical outcomes". The quality rating is listed for each clinical study in the Master Clinical Table, Appendix D.

A further 20 publications report studies directly assessing the relationship between the total quantity of phosphorus in the diet and clinical outcomes without allowing differentiation between food-additive and nonfood-additive phosphorus. None of the studies provided evidence of high quality, 15 provided evidence of moderate quality, and 5 provided evidence of low quality. These publications are summarized in Section "Total dietary phosphorus and clinical outcomes".

The 22 studies, sorted by area of investigation, are characterized in Table 8. All were observational studies: 15 were prospective cohort studies, 4 were case–control studies, and 3 were cross-sectional studies. Of the 22 studies, 10 examined the association of dietary phosphorus intake with the occurrence of cancers, 4 with all-cause mortality, 2 with physical performance, 3 with bone fracture, and 1 each with multimorbidity, dental caries, and timing of menarche.

These studies are discussed in Section "Food–additive phosphate and clinical outcomes" and Section "Total dietary phosphorus and clinical outcomes" and its subsections, and a brief review of the evidence the studies provide is presented in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes".

Several of the research articles contain summaries of the evidence and lists of other articles already available at the time they were published: some of these secondary references examine dietary components other than phosphorus, and not all of them are reviewed in the white paper. Among the publications containing useful summaries, discussions, and citation lists are the following: Chan and others (2000), Kesse and others (2006), Noori and others (2010a), and Tavani and others (2005). The article by Noori and others (2010), among other publications cited in this section, discusses possible mechanisms of toxicity of high dietary phosphorus intake.

Brief summaries of the reported studies, grouped according to study focus, are provided in the following subsections. The summaries are followed by Table 9, which provides further details on subject number, study population, adjustments made and covariates examined, method of determination of dietary phosphorus intake, and duration of follow-up where applicable. Several studies examined macronutrients and other micronutrients in addition to phosphorus, as well as intakes of whole foods or intakes within food categories; however, all the summaries focus on the information the studies provide relevant to dietary phosphorus intake and nutrient–nutrient interactions involving phosphorus. Several studies examined possible mediators of associations between phosphorus intake and morbidity or mortality, as well as the direct associations themselves. The summaries in the following 2 subsections focus on the direct associations, and the indirect associations are referred to in other sections of the white paper where they contribute to the discussions.

The papers by Noori and others (2010a) and Lynch and others (2011) examined dietary phosphorus intake in patients on hemodialysis. These papers are not discussed further in Section "Dietary phosphorus and clincial outcomes" but in Appendix A1.2.1.3.

Food-additive phosphate and clinical outcomes. Only 2 primary research publications included in the white paper focused on data that potentially allowed associations between a dietary food-additive phosphorus component and a clinical outcome to be assessed apart from associations of total dietary phosphorus intake. Both investigated relationships between cola consumption and bone fracture in children of school age. In neither publication was an attempt made to quantify the amount of phosphorus additive in the cola consumed nor to confirm its presence. Both mentioned phosphoric acid as a cola ingredient possibly contributing to the observed associations. Both studies presented evidence of low quality according to the rating scale employed in the white paper. In one additional publication, focusing on total dietary phosphorus intake, the investigators did not find an association between all-cause mortality and soda or fast food consumption in subjects with the highest intake of total dietary phosphorus (Chang and others 2014).

Ma and Jones reported a population-based case–control study examining associations of upper limb fracture risk with soft drink and milk consumption in children aged 9 through 16 y and exploring mediation of these associations by BMD, physical inactivity, or milk intake (Ma and Jones 2004). The study was conducted in 206 (single-site) fracture cases and 206 randomly selected matched controls in Southern Tasmania. A cola drink was defined as any cola-flavored carbonated beverage and a carbonated drink as any noncola carbonated drink. There were 47 hand fractures, 128 wrist and forearm fractures, and 31 upper arm fractures. The authors performed statistical adjustments in 4 steps. After adjustment for milk intake only (Step 1), the OR for cola drink consumption and wrist and forearm fracture risk was 1.43 (95% CI: 1.03 to 1.97; $P < 0.05$) per unit increase times of drinking cola per week; after making all specified adjustments (Table 9), the OR was 1.31 (95% CI: 0.94 to 1.83; $P \geq 0.05$). Total intake of carbonated beverages and intake of milk were not associated with fracture risk. On the basis of their analyses, the authors consider it most likely that television and video watching and computer use (each among the covariates taken into account) increase both fracture risk (for wrist and forearm fractures) and cola intake. Nevertheless, they conclude that their findings suggest that "cola but not milk and not carbonated beverage consumption is associated with increased wrist and forearm fracture in children, suggesting that consumption of cola drinks should be limited in children," while at the same time pointing to apparent "mediators" of this association, including low BMD and television, video, and computer watching, but not decreased milk intake. The authors state that a number of possible mechanisms have been put forward to explain the positive association between carbonated beverage consumption and risk of fracture, including replacement of milk in the diet by the beverage and a relatively high intake of caffeine, phosphoric acid, or sugar.

Wyshak (2000) reported a cross-sectional study examining the association between carbonated beverage consumption and bone fracture in teenage girls. The study included 460 teenage girls.

Table 8–Summary characteristics of studies: dietary phosphorus and clinical outcomes

Study reference	Study design	Area of investigation	Focus	Quality
Chang and others (2014)	Prospective cohort	All-cause mortality and cardiovascular mortality	–	Moderate
Noori and others (2010b)	Prospective cohort	All-cause mortality	–	Moderate
Murtaugh and others (2012)	Prospective cohort	All-cause mortality	–	Moderate
Lynch and others (2011)	Prospective cohort	All-cause mortality	–	Moderate
Ruel and others (2014)	Prospective cohort	Multimorbidity	–	Moderate
Elmståhl and others (1998)	Prospective cohort	Bone health	Fracture	Moderate
Ma and Jones (2004)	Case–control	Bone health	Fracture	Low
Wyshak (2000)	Cross-sectional	Bone health	Fracture	Low
Michaud and others (2000)	Prospective cohort	Cancer	Bladder	Moderate
Kesse and others (2005)	Prospective cohort	Cancer	Colorectal	Moderate
Boutron and others (1996)	Case–control	Cancer	Colorectal	Low
Merritt and others (2015)	Prospective cohort	Cancer	Endometrial	Moderate
Tavani and others (2005)	Case–control	Cancer	Prostate	Low
Chan and others (2000)	Prospective cohort	Cancer	Prostate	Moderate
Kesse and others (2006)	Prospective cohort	Cancer	Prostate	Moderate
Tseng and others (2005)	Prospective cohort	Cancer	Prostate	Moderate
Wilson and others (2015)	Prospective cohort	Cancer	Prostate	Moderate
Chan and others (1998)	Case–control	Cancer	Prostate	Low
Lin and others (2014)	Cross-sectional	Dental health	Caries	Low
Ramezani Tehrani and others (2013)	Prospective cohort	Growth and development	Menarche	Moderate
Sharkey and others (2003)	Cross-sectional	Physical performance	Lower extremities	Low
Scott and others (2010)	Prospective cohort	Physical performance	Muscle strength	Moderate

Relevant data from a self-administered questionnaire used in the course of a project to reduce teenage pregnancy were analyzed. Of all the girls surveyed, 79.1% drank carbonated beverages, 49.8% drank colas only, and 15.0% drank both cola and noncola carbonated beverages. Beverage consumption was not quantified in the analysis, for which all variables were dichotomized (for beverage classes, no consumption compared with some consumption; for fracture, negative compared with positive history; for physical activity, "vigorous" compared with "high-level"). The investigators noted a higher rate of fracture in girls who drank colas only than in those who drank no carbonated beverages: OR = 2.7 (95% CI: 1.30 to 5.60); $P = 0.008$. The OR for this association was of similar magnitude but not statistically significant when examined only in girls in the vigorous activity category or only in girls in the high-level activity category; for girls in the latter category, drinking of both cola and noncola beverages was associated with a higher risk of fracture: OR = 7.00 (95% CI: 2.00 to 24.45); $P = 0.002$.

Total dietary phosphorus and clinical outcomes. *All-cause mortality*. Two primary research articles other than the articles by Noori and others (2010a) and Lynch and others (2011), which report studies in hemodialysis patients and are considered further in Appendix A1.2.1.3, reported studies that examined associations between dietary phosphorus intake and all-cause mortality. Both present evidence of moderate quality according to the rating scale employed in the white paper.

Chang and others (2014) reported a prospective cohort study examining the association between total dietary phosphorus intake and all-cause and cardiovascular mortality. The study was conducted in 9686 healthy, nonpregnant adults aged 20 through 80 y selected from the NHANES III (1988 to 1994). Dietary nutrient and energy components and phosphorus intake were determined. Both absolute dietary phosphorus intake and phosphorus density were derived. The NHANES III mortality file was used to determine all-cause and cardiovascular mortality. The median follow-up time was 14.7 y. After making the specified adjustments (Table 9), the investigators reported a statistically significant association between higher absolute phosphorus intake at amounts greater than 1400 mg/d, consumed by 35.1% of the study population, and increased mortality (aHR [95% CI]: 2.23 [1.09, 4.55] per 1-unit increase in ln[phosphorus intake]; $P = 0.03$); and between higher dietary phosphorus density at levels greater than 0.35 mg/kcal and increased mortality (aHR [95% CI]: 2.27 [1.19, 4.33] per 0.1-mg/kcal increase; $P = 0.01$). In addition, a statistically significant association was detected between higher dietary phosphorus density and increased cardiovascular mortality but none between absolute phosphorus intake and cardiovascular mortality. All-cause mortality associated with the highest quartile of dietary phosphorus intake did not vary with soda consumption, fast food consumption, or the U.S. Department of Agriculture Healthy Eating Index score. The associations of absolute phosphorus intake and dietary phosphorus density, respectively, and all-cause mortality were unchanged when analyses included serum phosphorus concentration as a covariate, although higher serum phosphorus concentration was itself associated with increased mortality. The authors conclude that high phosphorus intake was associated with increased mortality in a sample of individuals, representative of the healthy population in the United States. They state further that this association is of concern because high dietary phosphorus intake is prevalent and that additional studies are needed to determine whether the association is causal.

Murtaugh and others (2012) reported a prospective cohort study examining the association between total dietary phosphorus intake and mortality in moderate CKD. The study was conducted in 1105 adults with early-stage III CKD selected from the NHANES III (1988 to 1994). The age of participants (mean ± SD) ranged from 70.8 ± 12.3 y in the lowest tertile of phosphorus intake to 67.4 ± 13.0 y in the highest tertile. The NHANES III Linked Mortality File was used to ascertain deaths. The mean follow-up time was 6.5 y and 592 (54%) deaths occurred. The authors used 4 statistical models. In the unadjusted model, each 100-mg/d increase of dietary phosphorus was associated with HR for death of 0.96, and the 95% CI excluded unity; in the fully adjusted model (Table 9); however, the HR for death (95% CI) was 0.98 (0.93, 1.03). Results were qualitatively similar when tertiles of phosphorus intake were examined, and there was no statistically significant association of intake tertile with mortality in the fully adjusted model: HR (95% CI) was 1.07 (0.67, 1.70) for highest tertile (daily phosphorus intake [mean ± SD] 1478 ± 28 mg/d) compared with the lowest tertile (531 ± 11 mg/d). An additional finding was a

Table 9–Subject number, study population, covariates examined, method of determination of dietary intake, and duration of follow-up

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Boutron and others (1996)	Total: 1269 • Adenoma part – Adenoma patients: 362 – Polyp-free controls: 427 • Cancer part: – Cancer patients: 171 – Controls: 309	Adenoma part • 30 to 75 y of age • Resident in the Côte d'Or area of Burgundy, France • Had undergone endoscopy • Exclusion criteria: – Familial polyposis coli – Hereditary nonpolyposis colorectal cancer – Colorectal tumor – Inflammatory bowel disease – Colectomy – Any type of cancer Cancer part • Cases recruited through all specialists in charge of such patients, with the help of the Registry of Digestive Tumours of Burgundy • Controls in the appropriate age group selected at random from a census list	• Age • Sex • Caloric intake	• Validated diet history method using a questionnaire to elicit data about the diet in the previous year • Followed the pattern of meals throughout the day • Administered by specially trained dietician, who coded the data • Food composition table containing data from available food composition tables and additional information from the food industry	NA
Chan and others (1998)	• 526 cases (mean age 70.6 y), 536 controls (mean age 70.7 y)	Cases (526) • All men under age 80, born in Sweden, and living in Örebro County, Sweden, with cytologically or histologically proven prostate cancer newly diagnosed at 1 of the 3 local hospitals • Majority of cases had prostate-related symptoms (screening not used in this area) Controls (536) • Men, frequency matched by age, randomly selected from the local population registry • Eligibility criteria – First 256 screened for prostate cancer and negative on biopsy if screening positive (3% positivity rate) – Responded to mailed questionnaire (approximately 80% response rate)	• Age • Family history of prostate cancer • Cigarette smoking • Energy intake	• Validated and reproducible self-administered food frequency questionnaire • Diet in preceding year assessed • Portion sizes taken from the Swedish National Food Administration handbook	NA
Chan and others (2000)	27062	• 27111 men who completed dietary questionnaires identified from the 29133 participants in the in the ATBC, a study on lung cancer incidence conducted among male smokers residing in southwestern Finland, in which participants were randomized to receive alpha-tocopherol and beta-carotene using a 2 × 2 design • Exclusion criteria from ATBC – History of cancer or other serious disease limiting participation – Further exclusion criteria from Chan study – Unknown stage or Stage 0 or Stage 1 incident prostate cancer	• ATBC study arm assignment • Education • Age • BMI • Energy • Number of years as smoker	• Validated and reproducible food frequency questionnaire, including portion sizes • Self-completion of questionnaire with subsequent review by study nurse together with participant • Data collected for the preceding 12 mo	Approximately 8 y

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

(Continued)

Table 9–Continued

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Chang and others (2014)	9686	• 12366 potential participants initially identified from the NHANES III 1988 to 1994 • Approximately 2600 excluded on the following grounds: – Insufficient data related to diet or the covariates examined – Presence of diabetes history of specified cardiovascular diseases or cancer – "Extreme energy intakes" vital status could not be determined	• Self-reported age • Sex • Race • Ethnicity • Cigarette smoking • Physical activity • Family income • Physical activity • Cardiovascular risk factors • Kidney function • Energy intake	• Application of the United States Department of Agriculture Survey Nutrient Database to 24-h dietary recalls administered to participants face-to-face by trained interviewers • Soda consumption quantified and fast foods identified according to set criteria • Food group consumption and overall quality of diet quantified, the latter using the USDA Healthy Eating Index	Median: 14.7 y
Elmståhl and others (1998)	6576	Random sample of men selected from 53000 men and women born between 1926 and 1945 and resident in Malmö, Sweden	For multivariate adjusted RR: • Age • Education • Marital status • Ethnicity • Physical activity at work • History of myocardial infarction, stroke, or hypertension • Smoking • Intakes of energy, fat, vitamin D calcium, zinc, and phosphorus	• Modified diet history method, assessed for validity and reproducibility, combining a 7-d menu book and a quantitative food frequency questionnaire • Data collected for the previous year • Usual portion sizes estimated • Data coded using the Swedish Food Data Base from the National Food Administration	Mean observation time: 2.4 y
Kesse and others (2005)	Adenoma study: • With adeno-matous polyps: 516 • Polyp-free: • 4804 • Colorectal cancer study: • With colorectal cancer: 172 • Free of colorectal cancer: 67312	100000 women living in France, aged 40 to 65 y at baseline and insured with a national health insurance scheme for teachers (the cohort of the E3N-EPIC prospective Exclusion criteria: • Adenoma study – Extreme values for energy intake to energy requirement ratio – Previous cancer – Familial adenomatous – Inflammatory bowel disease – Personal history of previous adenoma – Adenoma diagnosed after the end of follow-up • Colorectal cancer study: – Extreme values for energy intake/energy requirement ratio – Cancer diagnosis before the start of follow-up – Nonhistologically confirmed colorectal cancers – Familial polyposis syndrome – Inflammatory bowel disease – Lost to follow-up after dietary assessment	• Total dietary energy intake • BMI • Total daily alcohol free energy intake and total daily alcohol intake • Family history of colorectal cancer • Physical activity • Education level • Smoking status • Calcium or vitamin D • Fiber and folate • Consumption of red meat • Consumption of processed meat • Contribution of saturated fatty acids to dietary energy intake	• Validated dietary questionnaire administered at baseline • Dietary intake of calcium, vitamin D, and phosphorus and calcium to phosphorus ratio analyzed using food composition table derived from the French national database	Median: • Adenoma study: 3.7 y Cancer study: 6.9 y

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

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Table 9–Continued

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Kesse and others (2006)	2776	• 2805 men identified from the 12741 participants in the SU.VI.MAX trial, which assessed the primary prevention of cancers and ischemic heart disease through supplementation of minerals (selenium and zinc) and antioxidant • Subjects identified on the basis that they had completed least 5 dietary records over the 1st 18 mo of SU.VI.MAX • Subjects excluded from the final analysis if they reported a cancer diagnosis before the start of follow-up, were lost to follow-up during the dietary data assessment period, or developed cancer other than prostate cancer	• Energy intake • BMI • Daily alcohol intake • Family history of prostate cancer • Physical activity level • Occupation • SU.VI.MAX treatment group • Smoking status • Other potential confounders, such as consumption of saturated fatty acids, vegetables, and meat also tested • All variables assessed at baseline	• Consumption of certain specific dairy products (yogurt, fresh cheese, milk, and cheese) and of total dairy products assessed • Dietary intake of calcium and phosphorus was calculated using a food composition table	Median: 7.7 y
Lin and others (2014)	2248	• 24 students from each of 104 schools randomly selected using the database of the Nutrition and Health study, a population-based survey investigating the nutrition and health status of elementary schoolchildren in Taiwan	For ANCOVA models (nutrient means) and logistic regressions (ORs for dental caries): • Sex • Age • Birth rank • Parental education level • BMI • Sweet intake • Tooth brushing habits • Fluoride exposure	• 24-h dietary recalls and food frequency questionnaires administered in person to children and parents jointly by trained interviewers • Quantities of different foods consumed estimated using various tools • Assessment of Chinese Dietary Intake system together with major Taiwanese nutrient databases then applied • Information about snacks and beverages collected through food frequency questionnaire	NA
Ma and Jones (2004)	412	• Cases were subjects aged 9 through16 y with a single-site upper limb fracture identified from a Southern Tasmanian fracture registry. 206 cases eligible after application of the following exclusion criteria: – Presence of diseases that would prevent completion of the protocol – Migration out of the study area – Not enrolled in school – Previous upper limb fracture at ages 9 through 16 y – Nonresponders whose fractures were >3 mo past the date of fracture were excluded. • 206 controls were sex matched and randomly selected from the same school class as the paired case. – Exclusion criterion: upper limb fracture at ages 9 through 16 y	For "Step 4": • Milk intake • Television, computer, and video watching • Lumbar spine bone apparent mineral density • Metacarpal morphometry	• Nonvalidated food frequency questionnaire administered face-to-face with assistance from parent or guardian • Frequency determined of dairy, cola, and total carbonated drinks in a normal week during the preceding year • Serving size indicated to be 300 mL • Cola drink defined as any cola-flavored carbonated beverage and carbonated drink as any noncola carbonated drink	NA

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

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Table 9–Continued

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Merritt and others (2015)	• EPIC: 301107 • NHS and the NHSII: 155406	EPIC: • 367903 potential (women) participants initially identified • 66796 participants excluded on the following grounds: – Reported a prevalent cancer – Missing follow-up – Had a hysterectomy – Did not complete a dietary or lifestyle questionnaire extreme energy intake to energy requirement ($n = 6045$) – Had outlying nutrient intake values NHS and NHSII: • 238130 potential participants initially identified • 82724 participants excluded on the following grounds: – Diagnosis of cancer – Those who had died – Reported a hysterectomy – Ineligible (for example, duplicate id) – Also excluded from cycles where BMI was missing or had an extreme caloric intake	For "Model 2": • BMI • Total energy • Smoking status • Age at • Oral contraceptive use • Menopausal status and postmenopausal hormone use • Parity • Stratification by age at recruitment and the study center • Total energy intake	EPIC: • Validated dietary questionnaires or food records • EPIC Nutrient Database used to calculate standardized nutrient intake NHS and NHSII: • Validated and reproducible food frequency questionnaire administered at baseline and every 4 y thereafter • United States Department of Agriculture food composition data	• EPIC: mean 11 y • NHS and NHSII: mean 25 y
Michaud and others (2000)	47909	• 51529 participants in the Health Professionals Follow-Up Study – Cohort initiated in 1986 – Predominately white men aged 40 to 75 y • Criteria for exclusion from bladder cancer study: – Implausibly scores for total food intake – Incomplete baseline dietary questionnaire Missing date of birth – Preexisting cancer	• Total energy intake • Age • Smoking • Total fluid • Intake • Cruciferous vegetable intake • Geographic region	• Previously validated dietary questionnaire • Data from the 1986 questionnaire used in the main analysis • Food composition data primarily based on the United States Department of Agriculture Nutrient Database for Standard Reference	Not reported explicitly (maximum: 12 y)
Murtaugh and others (2012)	1105	• 16864 with valid data for estimation of the glomerular filtration rate identified from NHANES III (1988 to 1994) • Inclusion criteria – Chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2) – Nonmissing data for dietary intake, nutritional variables, and mortality	For "fully adjusted" model: • Energy intake • Age • Sex • Race • Comorbid conditions • Lifestyle • Dietary variables • Estimated glomerular filtration rate • Nutritional variables	• Application of the United States Department of Agriculture Survey Nutrient Database to 24-h dietary recalls administered to participants by trained interviewers using a computer-based interview system	Mean: 6.5 y

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

(Continued)

Table 9–Continued

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Ramezani Tehrani and others (2013)	134	• Participants selected from the 15000 participants in the TLGS, a representative sample of the Tehran population 3 y of age and older • 1474 TLGS participants had dietary data collected at baseline • 190 were girls in the targeted age range	• Energy intake per cm of height and dairy or other nutrients intake per 1000 Kcal of energy intake • Age • Baseline energy and protein intake • Interval between the age at study initiation and the age of menarche • Maternal age at menarche • *Z*-scores for baseline BMI and height	• Assessment at baseline by expert dieticians • Dietary recalls for two 24-h periods approximately 10 d apart	Median: 6.5
Ruel and others (2014)	1020	• Complete dietary information available for 2849 individuals from the Jiangsu Province of the Chinese National Nutrition and Health Survey, which represented a geographically and economically diverse population • Inclusions criteria: – Participated in follow-up interview – Required information available for each chronic disease examined both at baseline and follow-up	For "fully adjusted" model: • Energy intake • Age • Sex • Smoking status • Annual income • Marital status • Education • BMI • Sedentarity	• Three-day weighted food record assessed at baseline • Three consecutive days, including 1 weekend day • Macronutrient and micronutrient composition determined by using the Chinese Food Composition Table	Approximately 5 y
Scott and others (2010)	740	• Participants selected from the prospective population-based Tasmanian Older Adult Cohort Study, which enrolled a sex-stratified random sample of community-dwelling persons aged 50 to 79 y • Exclusion criteria: – Contraindication to magnetic resonance imaging – Institutionalization – Failure to complete follow-up visit – Nonperformance of leg strength test – Incomplete data	For longitudinal multivariate analyses • Age • Sex • Physical activity • Body fat • Baseline appendicular lean mass • Protein intake • Energy intake	• Validated self-administered food frequency questionnaire • Questionnaire checked by an interviewer to ensure correct completion	Mean observation time: 2.6 y (range 1.4 to 4.8 y)
Sharkey and others (2003)	321	• Participants selected from the 348 participants in the NAFS, a study of recipients of home-delivered meals who were aged ≥60 y and were homebound as a result of disability, illness, or isolation • participant in NAFS excluded from the analysis if they were not ambulatory or otherwise unable to stand for weight determination	Model used controlled for the following confounders: • Demographic characteristics • BMI • Health characteristics	• Three 24-h dietary recall questionnaires administered by trained interviewers • Portion size estimated and the Nutrition Data System for Research used to calculate nutrient intakes • Nutrient estimates included meal supplements (for example, Ensure) but not vitamin and mineral supplements	NA

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

(Continued)

Table 9–Continued

Study reference	Number of subjects	Study population	Adjustments and covariates[a]	Method of determination of dietary intake	Duration of follow-up
Tavani and others (2005)	2745	Cases (1294) • Men admitted to the major teaching and general hospitals in the areas under surveillance with incident histologically confirmed prostate cancer Controls (1451) • Men residing in the same areas and admitted to the same network of hospitals for a wide spectrum of acute conditions • Exclusion criterion – Condition related to known or likely risk factors for prostate cancer – Conditions potentially influencing dietary habits	• Age • Center • Education • BMI • Tobacco smoking • Physical activity • Total energy intake • Family history of prostate cancer in first degree relative	• Validated and reproducible food frequency questionnaire administered by trained interviewers • Data collected for the 2 y preceding the onset of the disease leading to admission • Intake of selected nutrients and total energy calculated using Italian food composition databases	NA
Tseng and others (2005)	3612	• Selected from all 5811 males participating in the 1st National Health and Nutrition Examination Epidemiologic Follow-Up Study (14407 participants in all, aged between 25 and 74 y, representative of the noninstitutionalized civilian population of the United States) • Potential participants excluded: – Died before the baseline interview – Not traced or not interviewed – Diagnosis of prostate cancer at or before baseline interview – Did not complete the diet questionnaire – Extreme energy intakes	• Age • Race • Energy intake • U.S. region • Rural, urban, or suburban residence • Education • Sun exposure • Level of physical activity smoking status • Current alcohol intake • Poverty census enumeration district • Family income	• Food-frequency questionnaire (not validated) administered at baseline (1982 to 1984) • Nutrient content and portion size based on 24-h recall data from the 2nd NHANES • Participants asked about current (1982 to 1984) use of multivitamins and of any other vitamins, minerals, or nutritional supplements	Mean: 7.7 y (range: <1 to 10.7 y)
Wilson and others (2015)	47885	• Participants selected from the 51529 participants (all men) in the Health Professionals Follow-Up Study • Inclusion criterion – Men who adequately – completed the baseline food-frequency questionnaire • Exclusion criteria – Men who reported a diagnosis of cancer before baseline	For the "fully adjusted model": • Age • Calendar time • Race • Height • BMI at age 21 y and current • Vigorous physical activity • Smoking • Diabetes • Family history of prostate cancer • Intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol • Energy intake • Multivitamin use • History of prostate specific antigen testing	• Validated semiquantitative food frequency questionnaire administered at baseline and every 4 y thereafter • Multivitamins and calcium supplement use assessed • Nutrient intakes calculated by multiplying frequency of consumption by the serving size and the nutrient content of the food • Processed meat consumption estimated as the sum of servings per day of sausage, salami, bologna, hot dogs, and bacon	24 y
Wyshak (2000)	460	• Ninth and 10th graders in an urban high school who completed a questionnaire in the course of a project designed to reduce teenage pregnancy	None described	• Self-administered questionnaire monitored by classroom personnel in a classroom setting • Author states that "on the whole, the responses were complete, internally consistent, and had face validity."	NA

ANCOVA, analysis of covariance; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BMI, body mass index; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); EPIC, European Prospective Investigation into Cancer and Nutrition study; NA, not applicable; NAFS, Nutrition and Function Study; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; RR, relative risk; TLGS, Tehran Lipid and Glucose Study; USDA, United States Department of Agriculture.

[a]Only variables other than the primary variables of interest are listed: for example, for the publication by Chan and others (2000) (title: Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus [Finland]) calcium and phosphorus are not among the variables listed in the table.

statistically significant, but "very modest," increase in serum phosphorus concentration with increasing dietary phosphorus intake. In the authors' opinion, these results suggest that, in early-stage III CKD, higher dietary phosphorus intake is not associated with increased mortality.

Cancer risk. Ten primary research articles reported studies that examined associations between dietary phosphorus intake and cancer risk. Six of the studies examined prostate cancer, 2 examined colorectal cancer, and 1 each endometrial and bladder cancer. Of the 10 articles, 3 present evidence of low quality, and 7 present evidence of moderate quality, according to the rating scale employed in the white paper.

Prostate cancer. Of the 6 studies examining prostate cancer, 4 were prospective cohort studies and 2 were case–control studies. The former provide evidence of moderate quality, and the latter provide evidence of low quality, according to the rating scale employed in the white paper.

Wilson and others (2015) reported a prospective cohort study examining the association between calcium and phosphorus intake and prostate cancer. The study was conducted in 47885 men aged 40 to 75 y at baseline selected from participants in the Health Professionals Follow-Up Study. Incident cases of prostate cancer were identified through self-report by participants or next of kin on biennial questionnaires and confirmed through inspection of medical records and pathology reports. Deaths were reported by family members or identified through the National Death Index, and cause of death was determined by an adjudication committee based on registry information, medical history and records, death certificates, and all other available relevant data. The follow-up time was 24 y, during which 5861 cases of prostate cancer were identified. Several statistical models were used. After making adjustments according to the "fully adjusted" model (Table 9) and adjusting for calcium intake, the RR for all prostate cancers for participants in the highest quintile of dietary phosphorus intake (mean intake 1783 mg/d) relative to those in the lowest quintile (mean intake 1079 mg/d) was 1.11 (95% CI: 1.00 to 1.24; $P = 0.04$ for trend across all quintile); the RR for the prostate cancer subtype, high-grade cancer, was 1.50 (95% CI: 1.09 to 2.08; $P = 0.006$ for trend). For each of the subtypes, lethal cancer (defined as death or distant metastases), advanced-stage cancer, localized cancer, Grade 7 cancer, and low-grade cancer, P for trend was greater than 0.05 in the fully adjusted model after adjustment for calcium intake. In the authors' opinion, a latency analysis suggested an independent effect of phosphorus and of calcium on advanced-stage and high-grade prostate cancer: higher calcium intake was associated with increased risk only after 12 to 16 y, whereas higher phosphorus intake was associated with increased risk within 8 y after exposure. The correlation of phosphorus intake with fish consumption and white meat consumption were both positive; with red meat consumption, negative; and with processed meat consumption (sausage, salami, bologna, hot dogs, and bacon), negative. The authors advised that their "findings should be interpreted cautiously" because of high correlations in the study between the intakes of calcium and phosphorus, between these intakes and dairy consumption, and between phosphorus intake and meat consumption.

Kesse and others (2006) reported a prospective cohort study examining the association between the intake of dairy products, calcium, and phosphorus and the risk of prostate cancer. The final study analysis included 2776 men selected from participants in a trial assessing the primary prevention of cancers and ischemic heart disease through supplementation of minerals and antioxidants. Incident cases of prostate cancer were self-reported by participants and confirmed through retrieval of medical data and examination of official death certificates. The median follow-up time was 7.7 y, during which 69 diagnoses of prostate cancer were made. After making specified adjustments (Table 9), the investigators noted that the risk of prostate cancer increased with increasing intake of calcium, but the association was statistically significant only for calcium from dairy sources. The multivariate RR for prostate cancer in the highest (>1434 mg/d) compared with the lowest (<1167 mg/d) quartile of phosphorus intake (undifferentiated as to dietary source) was 1.83 (95% CI: 0.89 to 3.73), with $P = 0.04$ for trend across all quartiles. The investigators also considered the dietary calcium to phosphorus ratio. There was a significant interaction between phosphorus and calcium intakes and the correlation coefficient between calcium intake and phosphorus intake was 0.81. The investigators report that a high calcium intake appeared to be associated with a slightly higher risk of prostate cancer among subjects with a low phosphorus intake, but this association was not determined to be statistically significant. For dairy products, only yogurt showed a statistically significant association with prostate cancer risk in the multivariate analysis, with higher consumption being associated with increased risk. The authors considered the main finding of the study to be a relationship between calcium intake and the risk of prostate cancer, which they thought might be modulated by phosphorus intake.

Tseng and others (2005) reported a prospective cohort study examining the association between dairy, calcium, and vitamin D intakes and prostate cancer risk. The association of phosphorus intake and prostate cancer risk was also assessed. The study was conducted in 3612 men (mean [SD] age: 57.8 [14.6] y) selected from the 1st National Health and Nutrition Examination Epidemiologic Follow-up Study. Incident cases of prostate cancer were reported at any of 3 follow-up interviews; ascertained as a hospital discharge diagnosis during the follow-up period; or ascertained as a cause of death on death certificates obtained through tracing using the National Death Index or by other mechanisms. The mean follow-up time was 7.7 y (range: <1 to 10.7) and 136 cases of incident prostate cancer were diagnosed. After making the specified adjustments, a strong association was detected between dairy food intake and prostate cancer risk, and between dietary calcium intake and prostate cancer risk. No association was found between dietary phosphorus intake and prostate cancer risk when calcium was also considered: the adjusted RR for prostate cancer in the highest (median phosphorus intake: 1443 mg/d) compared with the lowest (984 mg/d) tertiles of phosphorus intake was 0.9 (95% CI: 0.5 to 1.6), with $P = 0.77$ for the trend across all tertiles.

Chan and others (2000) reported a prospective cohort study examining associations between diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus. The study was conducted in 27062 men between the ages of 50 and 69 y at baseline selected from among participants in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, a study on lung cancer incidence conducted among male smokers residing in southwestern Finland. Incident cases of prostate cancer were identified from the Finnish Cancer Registry and the Register of Causes of Death, and verified through review of medical records and histopathological and cytological reviews. The follow-up time was approximately 8 y, during which 184 cases of Stages 2 through 4 prostate cancer (American Joint Committee on Cancer 1992 criteria) were identified. A further 49 cases (both the

cancers and the persons in whom they developed) were excluded from the analysis because the cancers were Stage 0 or Stage 1 (48 cases) or of unknown staging (1 case). The authors observed no association for phosphorus and total prostate cancer risk in the standard multivariate model used. After making the specified adjustments (Table 9), the multivariate RR for Stages 2 through 4 prostate cancer for participants in the highest quintile of dietary phosphorus intake (median intake: 2468 mg/d) relative to those in the lowest quintile (median intake: 1655 mg/d) was 1.1 (95% CI: 0.7 to 1.8; $P = 0.45$ for trend across all quintile); these finding were not qualitatively changed by controlling for calcium intake. Cross-categorization of the study population by energy-adjusted calcium and phosphorus intakes showed a multivariate RR of 0.6 (95% CI: 0.3 to 1.0) in the 11% of the study population who had higher phosphorus (cutoff point: 2091 mg/d) and lower calcium intakes (cutoff point: 1338 mg/d); $P = 0.09$ for interaction.

Tavani and others (2005) reported a case–control study examining the association between intakes of calcium, vitamin D, and phosphorus and the risk of prostate cancer. The study was conducted in 2745 men, aged 46 to 74 y in 4 areas of Italy. The multivariate OR for prostate cancer for participants in the highest quintile of dietary phosphorus intake (>1897 mg/d) relative to those in the lowest quintile (<1204.66 mg/d) was 1.20 (95% CI: 0.79 to 1.84; $P = 0.39$ for trend across all quintiles). The authors concluded that, at levels consumed in the study population, there was no evidence of an association between dietary phosphorus intake and the risk of prostate cancer.

Chan and others (1998) reported a case–control study examining the association between intakes of dairy products, calcium, phosphorus, and vitamin D and the risk of prostate cancer. The study was conducted in 1062 men with a mean age of 70.65 living in Sweden. The multivariate OR for prostate cancer for participants in the highest quartile of dietary phosphorus intake relative to those in the lowest quartile was 0.67 (95% CI: 0.44 to 1.02). When a continuous measure was used, dietary phosphorus intake was not associated with risk of prostate cancer ($P = 0.22$) in a model which included age, family history of prostate cancer, smoking, total calories, calcium, phosphorus, and vitamin D. Consumption of dairy foods was associated with a higher risk of prostate cancer, and this association was stronger when the analysis was confined to data from men with advanced stages of prostate cancer. The authors concluded that calcium, in conjunction with phosphorus, may be a critical component in the association of dairy foods with prostate cancer.

Colorectal cancer. Two studies examined colorectal cancer; one a prospective cohort study (Kesse and others 2005) and the other a case–control study (Boutron and others 1996). The former provided evidence of moderate quality, and the latter provided evidence of low quality, according to the rating scale employed in this white paper.

Kesse and others (2005) reported a prospective cohort study examining the association between dietary calcium, phosphorus, vitamin D, and dairy products, and the risk of colorectal adenoma and cancer. The study was conducted in 100000 women living in France, aged 40 to 65 y at baseline. The study had 2 parts: one, with median follow-up time of 3.7 y, examining incident cases of histologically confirmed adenomatous polyps (516 cases after application of specified exclusion criteria); and the other, with median follow-up time of 6.9 y, examining incident cases of histologically confirmed colorectal cancer (172 cases after application of specified exclusion criteria). Subjects with adenomatous polyps were compared with subjects who were colonoscopically polyp-free at study end (4804 women); subjects with colorectal cancer were compared with subjects who were free of cancer (67312 women). After making the specified adjustments (Table 9), the investigators detected a statistically significant association between increasing dietary phosphorus intake and decreasing RR of (all) adenomas: the RR for adenoma in the highest (>1634 mg/d) compared with the lowest (<1142 mg/d) quartile of phosphorus intake was 0.7 (95% CI: 0.54 to 0.90), with $P = 0.005$ for trend across all quartiles. There were similar trends for high-risk adenoma and for colorectal cancer but these were not statistically significant. Interaction between dietary phosphorus and calcium was noted to be statistically not significant, although the authors comment that intakes of phosphorus and calcium were strongly correlated in the study population and that the observed protective effects of calcium and phosphorus, respectively, might have partially confounded each other. The RR of adenoma was also decreased with increasing intake of total dietary calcium, and this decrease was statistically significant.

Boutron and others (1996) reported a case–control study examining the association between intakes of calcium, phosphorus, vitamin D, and dairy products and colorectal carcinogenesis. The Ca:P ratio was also examined. The study was conducted in 2 separate populations, in one of which (789 persons) risk factors for colorectal adenomas were examined and, in the other (480 persons), risk factors for colorectal cancer. Sample size calculations were based on fat intake. The authors did not observe an association between high dietary intake of phosphorus or low calcium to phosphorus ratio and the risk of adenomas. They report "a trend toward an increased risk of colorectal cancer associated with phosphorus intake in women (OR, 3.5; 0.8 to 15.9; P for trend 0.08), but not in men (OR, 1.4; 0.4 to 4.7)." For men and women together, the OR for colorectal cancer for participants in the highest quintile of dietary phosphorus intake (>2038.7 mg/d for men and >1554.3 mg/d for women) relative to those in the lowest quintile (<1241.9 mg/d for men and <1003.4 mg/d for women) was 1.9 (95% CI: 0.8 to 4.6; $P = 0.17$ for trend across all quintiles). The authors reported further that "the highest level of the calcium to phosphorus ratio yielded an OR of 1.3 [for colorectal cancer] in both men and women ($P > 0.10$)." They did not observe any modulation by phosphorus intake of the association between dietary calcium intake and colorectal tumors.

Urogenital cancer other than prostate cancer. Two studies examined urogenital cancers other than prostate cancer. Both were prospective cohort studies and both provided evidence of moderate quality according to the rating scale employed in this white paper.

Merritt and others (2015) reported an investigation of the association between dietary factors and endometrial cancer risk in participants in 3 prospective cohort studies: the European Prospective Investigation into Cancer and Nutrition (EPIC) study, the Nurses' Health Study (NHS), and the Nurses' Health Study II (NHSII). Analysis of data from the EPIC study allowed selection of factors for validation in the NHS and the NHSII. Data were included from 301107 female EPIC study participants aged 25 through 70 y at enrollment; and from 155406 NHS and NHSII participants (all women) aged 25 through 55 y at enrollment. In the EPIC study, incident cases of endometrial cancer were identified through population-based registries or active follow-up, and mortality data were obtained from cancer and mortality registries. The mean follow-up time was 11 y. After censoring for

tumors that were not the 1st incident tumor, were nonepithelial, or were missing tumor behavior information, 1303 cases were identified. In NHS and NHSII, incident cases were self-reported by participants in biannual questionnaires and confirmed by using medical records and pathology reports. The mean follow-up time was 25 y, and a total of 1531 cases of confirmed epithelial endometrial cancer were identified. After adjustments for multiple comparisons, 10 of 84 foods and nutrients examined in the EPIC study were associated with incident endometrial cancer. After making the specified adjustments, the HR for endometrial cancer for participants in the highest quartile of dietary phosphorus intake (median intake: 1490 mg/d) relative to those in the lowest quartile (984 mg/d) was 0.82 (95% CI: 0.69 to 0.97; $P = 0.05$ for trend across all quartiles). However, this association was not confirmed among participants in the NHS and the NHSII: the HR for participants in the highest quartile of dietary phosphorus intake (1597 mg/d) relative to those in the lowest quartile (951 mg/d) was 1.05 (95% CI: 0.9 to 1.23; $P = 0.19$ for trend across all quartiles).

Michaud and others (2000) reported a prospective cohort study examining the association between dietary supplements, macronutrients, micronutrients (including phosphorus), and the risk of bladder cancer in men in the United States. The study included 47909 men. Incident cases of bladder cancer were self-reported by participants in questionnaires mailed to participants every 2 y and confirmed (where permission was obtained) through retrieval of medical data and examination of death certificates. The National Death Index was used to determine vital status for nonrespondents and detect bladder cancer cases previously unreported. The follow-up time is not reported explicitly but could not have exceeded 12 y for any participant: between 1986 and 31 January 1998, 320 cases of incident bladder cancer were diagnosed. Although the investigators found an inverse association between phosphorus intake and the risk of bladder cancer before adjusting for covariates, no association was observed when covariates were taken into account (RR 0.85; 95% CI: 0.57 to 1.21) for highest quintile of intake (median intake: 1728 mg/d) with respect to lowest quintile (1101 mg/d); P for trend = 0.4. The authors concluded that no association was observed in this study between macronutrient intake and bladder cancer.

Bone health. Three primary research articles reported studies that examined associations between dietary phosphorus intake and bone health.

The articles by Ma and Jones (2004) and Wyshak (2000), which potentially had a food-additive phosphorus dietary component, are discussed in the previous section. The 3rd publication is discussed in this subsection and presents evidence of moderate quality according to the rating scale employed in the white paper.

Elmståhl and others (1998) reported a prospective cohort study examining associations between intakes of phosphorus and zinc and fracture risk in middle-aged and elderly men. The study was conducted in 6576 men, aged 46 through 68 y, living in the city of Malmö, Sweden. Incident fractures were identified by using the registry of the Department of Radiology, Malmö University Hospital. All medical records associated with the X-ray examinations were evaluated. The mean observation time was 2.4 y. In total, 160 men had at least 1 fracture. After making the specified adjustments, the multivariate risks for fracture relative to the risk for participants below the 20th percentile of dietary phosphorus intake were as follows (percentile interval, RR [95% CI]): 21% to 40%, 0.50 (0.29, 0.87); 41% to 60%, 0.67 (0.37, 1.20); 61% to 80%, 0.56 (0.27, 1.16); 81% to 100%, 0.54 (0.23, 1.30). An analysis by quintile of phosphorus intake showed similar results, with a P for trend = 0.14. The cut point for the lowest quintile of phosphorus intake was 1357 mg/d, above the Swedish nutrient recommendations then current. The authors commented on the lack of a dose–response relationship between dietary phosphorus intake and fracture risk, with an apparent threshold effect.

Physical performance. Aging is associated with declining skeletal muscle mass and with growing impairment in muscle strength. Two studies evaluated the association of nutrition and specific dietary nutrients, including dietary phosphorus, with clinical outcomes, including muscle strength and physical performance. One was a cross-sectional study, and the other was a prospective cohort study: the former provided evidence of low quality and the latter provided evidence of moderate quality, according to the rating scale employed in the white paper. The study by Scott and others (2010) included muscle strength rather than a morbidity or mortality as an outcome, but is nevertheless included in this section.

Scott and others (2010) reported a prospective cohort study examining associations between dietary nutrient intake, including phosphorus intake, and muscle mass and strength in community-dwelling older adults. The study was conducted in 740 noninstitutionalized older adults (mean age at baseline: 62 y at baseline) in Southern Tasmania, Australia. The mean observation time was 2.6 y (range: 1.4 to 4.8 y), and in addition to the longitudinal analyses, cross-sectional analyses of baseline and follow-up data were conducted. After making the specified adjustments (Table 9), appendicular lean mass (aLM) at baseline was associated with dietary phosphorus intake in the multivariate analysis ($P < 0.001$ for trend across quartiles of phosphorus intake); in addition, calculation of regression coefficients showed that change in aLM over the follow-up period was associated with dietary phosphorus intake both before and after adjustment for protein intake (before: β coefficient = 0.07; $P = 0.03$; after: β coefficient = 0.07; $P = 0.047$). However, no associations were demonstrated between energy-adjusted nutrient intake and knee extension strength in cross-sectional or longitudinal analyses.

Sharkey and others (2003) reported a cross-sectional study examining the association between musculoskeletal nutrient intakes (including phosphorus) and lower extremity physical performance in a population at increased risk for poor nutritional status and functional decline, namely, homebound elderly persons, many of whom were poor, black, undereducated, and lived alone. The study included 321 men and women. Measures of static and dynamic balance in the standing position, usual walk speed, and repeated chair stands were used to calculate a summary of lower-extremity performance score. The investigators reported that a summary musculoskeletal nutrient score, calculated by adding quartiles of intake for calcium, vitamin D, magnesium, and phosphorus, was associated with measures of lower extremity physical performance: the OR (95% CI) for having the worst level of lower-extremity physical performance for persons in the lowest category of musculoskeletal nutrient scores was 1.88 (1.08, 3.27) with respect to those in the highest nutrient score category ($P \leq 0.05$). The RDA of phosphorus was specified to be 700 mg/d. The mean (±SD) percentage of RDA of phosphorus in the diet of subjects was 161.6% ± 46.3% for men and 124.8% ± 39.2% for women; 82 (26%) of subjects had diets containing less than 105% of RDA, and 81 (25%) of subjects had diets containing more than 154% of RDA. The difference in the percentage of RDA of dietary phosphorus was statistically significantly greater in men than in women ($P < 0.001$ [Student's t-test]).

Growth and development and child dental health. Two studies examined, respectively, associations between dietary phosphorus intake and dental health, and between dietary phosphorus intake and growth and development. The former was a cross-sectional study and provided evidence of low quality according to the rating scale employed in the white paper, and the latter was a prospective cohort study and provided evidence of moderate quality.

Lin and others (2014) reported a cross-sectional study examining the association between dietary calcium, phosphorus, and magnesium intake and dental caries' status among school children aged 6 through 12 y in Taiwan. The study included 1196 boys and 1052 girls. Each participant was interviewed in person and underwent a dental examination. Two systems were used to assign dental caries' scores to participants: the decay-missing filled teeth index used to assess the status of permanent teeth and the decayed tooth, decayed tooth indicated for extraction, filled tooth ("deft") index used to assess the status of the primary teeth. The decay-missing filled teeth scores and the deft scores were grouped separately (3 categories for each score). The authors performed 2 types of analysis. In the 1st, they considered mean nutrient values in each category. In the 2nd, they divided scores into those indicating no affected teeth and those indicating one or more affected teeth; and divided nutrient intakes into those that met the levels recommended in the 2002 Taiwanese Dietary Reference Intakes and those that did not. After making selected statistical adjustments (Table 9), neither analysis revealed an association between dental caries and dietary phosphorus intake. However, each analysis revealed that higher caries' scores were associated with lower dietary calcium to phosphorus ratios: in a multivariate analysis of the intakes of calcium, phosphorus, magnesium, and the calcium to phosphorus ratio, the OR (95% CI) for developing dental caries in the primary teeth for children with lower calcium to phosphorus intake ratios was 0.52 (95% CI: 0.30 to 0.90; $P = 0.02$) compared to those with higher ratios; and the OR for developing caries in permanent teeth was 0.59 (95% CI: 0.37 to 0.93; $P = 0.02$).

Ramezani Tehrani and others (2013) reported a prospective cohort study examining the association between menarcheal age and prepubertal intakes of specified dairy products and minerals. The study was conducted in 134 healthy prepubertal girls aged 4 through 12 y at baseline. Age at menarche was documented in completed whole years and ORs were calculated for menarche at ≤12 y of age. The median follow-up time was 6.5 y. After making the specified adjustments, the ORs for earlier menarche associated with age-adjusted intakes of the dairy products examined were statistically nonsignificant, whereas those associated with calcium, magnesium, and phosphorus, respectively, were statistically significant. When phosphorus intake was adjusted for age at baseline, an intake of >647 mg/d compared to ≤647 mg/d was associated with an OR for menarche at ≤12 y of age of 3.43 (95% CI: 1.45 to 8.13; $P = 0.005$). The authors concluded that the study provided evidence that "milk intake in prepuberty might hasten the timing of menarche." Furthermore, they stated that early menarche is a risk factor for breast cancer, Type 2 DM, metabolic syndrome, CVD, CVD mortality, and all-cause mortality: they supported this statement with citations provided in the report.

Multimorbidity. One study, a prospective cohort study, examined associations between dietary phosphorus intake and "multimorbidity." The study provided evidence of moderate quality according to the rating scale employed in the white paper.

Ruel and others (2014) reported a prospective cohort study examining the association between foods, macronutrients, and micronutrients and the evolution of multimorbidity. The study was conducted in 1020 adults (mean age [±SD]: 49 [13] y) randomly selected from 6 counties of Jiangsu Province, in the People's Republic of China. The term *multimorbidity* was defined as 2 or more of the following 11 chronic conditions: anemia, hypertension, hypercholesterolemia, diabetes, arthritis, hepatitis, CHD, asthma, stroke, fracture, and cancer. Health status was determined at baseline in 2002 and again in 2007, and diet was determined at baseline only. Physical examination and interview by health professionals, laboratory tests, and self-report were variously used to determine health status. Initial health status and subsequent changes were characterized using 6 "steps" (the term used by the authors of the report): (1) healthy; (2) healthy to first disease; (3) stable with one disease; (4) healthy to multimorbidity; (5) stable with multimorbidity; and (6) increasing multimorbidity. The association between evolution of multimorbidity and daily intake by food category was calculated from the 3-d weighted food records at baseline. Mean phosphorus intakes (±SD) for the 6 steps decreased with increasing morbidity, and were, respectively, 1119 ± 409, 1092 ± 370, 1012 ± 334, 1002 ± 308, 923 ± 234, and 987 ± 336 mg/d ($P \leq 0.001$ in the fully adjusted model [Table 9]). Overall, high intake of iron, magnesium, and phosphorus was associated with a healthier profile. The study noted that the daily intake in those micronutrients was higher in healthy individual than in those stable with one chronic disease, stable with multimorbidity, or with increasing multimorbidity ($P < 0.05$). The study reports a beneficial effect of the consumption of greater amounts of fruits and vegetables and grain products other than rice and wheat to prevent the evolution of multimorbidity. The consumption of grain products other than rice and wheat accounted for more than 24% of the magnesium, 32% of the phosphorus, and 21% of the iron intake.

Summary of evidence: total dietary phosphorus and clinical outcomes. Of the 20 studies summarized in Section "Dietary phosphorus and clincial outcomes" and in Table 9, half reported an association between dietary phosphorus and morbidity or mortality (Elmståhl and others 1998; Wyshak 2000; Sharkey and others 2003; Ma and Jones 2004; Kesse and others 2005; Kesse and others 2006; Ramezani Tehrani and others 2013; Chang and others 2014; Ruel and others 2014; Wilson and others 2015) and half did not find an association (Boutron and others 1996; Chan and others 1998; Chan and others 2000; Michaud and others 2000; Tavani and others 2005; Tseng and others 2005; Scott and others 2010; Murtaugh and others 2012; Lin and others 2014; Merritt and others 2015). In 6 studies, a higher intake of dietary phosphorus was associated with an increase in morbidity or mortality (Wyshak 2000; Ma and Jones 2004; Kesse and others 2006; Ramezani Tehrani and others 2013; Chang and others 2014; Wilson and others 2015) and in 4 studies with a decrease (Elmståhl and others 1998; Sharkey and others 2003; Kesse and others 2005; Ruel and others 2014). The study designs, clinical outcomes, and populations examined were diverse, as were their methods of dietary assessment and endpoint ascertainment, their durations of follow-up, their manipulation of data, and the statistical analyses they used to determine associations. The limitations that the characteristics of these studies place on the utility of the data they produced are discussed at several points in this section and discussed further in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies" and the subsections thereof.

Half (10) of the studies investigated possible associations between dietary phosphorus intake and cancer risk (Boutron and others 1996; Chan and others 1998, 2000; Michaud and others 2000;

Kesse and others 2005; Tavani and others 2005; Tseng and others 2005; Kesse and others 2006; Merritt and others 2015; Wilson and others 2015). An association (positive or negative) was detected in only 3 of these studies (Kesse and others 2005; Kesse and others 2006; Wilson and others 2015).

Higher dietary phosphorus intake was associated with an increase in cancer risk in 2 of the studies (Kesse and others 2006; Wilson and others 2015), both prospective cohort studies examining prostate cancer incidence. The other 4 prostate cancer studies reported no association (Chan and others 1998; Chan and others 2000; Tavani and others 2005; Wilson and others 2015). In one of the positive prostate cancer studies, the authors advise that their findings "should be interpreted cautiously" because of high correlations in the study between the intakes of calcium and phosphorus, between these intakes and dairy consumption, and between phosphorus intake and meat consumption (Wilson and others 2015). In the other positive prostate cancer study, the authors considered the main finding of the study to be a relationship between calcium intake and prostate cancer risk, a relationship that they considered might be modulated by phosphorus intake (Kesse and others 2006). The 3rd cancer study in which an association was reported investigated the incidence of colorectal cancer (Kesse and others 2005). In this prospective cohort study, higher dietary phosphorus intake was associated with a decreased incidence of colorectal adenoma in women; higher calcium intakes had a similar association. The other colorectal cancer study, a cross-sectional study in men and women, did not find an association of dietary phosphorus and cancer (Boutron and others 1996). The other cancer studies in which no association was indicated included one of endometrial cancer incidence (Merrit and others 2015) and one of bladder cancer incidence in men (Michaud and others 2000).

Three studies investigated associations between dietary phosphorus intake and bone health. One of these studies, in middle-aged and elderly men, reported a decrease in fracture risk with higher intakes of total dietary phosphorus (Elmståhl and others 1998). The other 2 studies focused on cola beverages, and both showed an increase in fracture risk with increasing intake of colas in school-aged children (Wyshak 2000; Ma and Jones 2004): these were the only 2 studies that focused on data potentially specific to a direct association between a phosphorus food additive (specifically, phosphoric acid) and a clinical outcome. An additional study investigated associations between dietary phosphorus intake and dental caries and found no association with phosphorus alone: however, lower dietary calcium to phosphorus ratios were associated with increased dental disease (Lin and others 2014).

Two studies investigated associations between dietary phosphorus intake and all-cause mortality, one in a population representative of the general U.S. population and one in a population with moderate CKD. The former followed over 9500 persons for an average of almost 15 y and determined that the risk of death increased 2.23-fold per 1-unit increase in ln(phosphorus intake) for absolute intakes greater than 1400 mg/d, intakes that were identified in over one-third of the study population (Chang and others 2014). The median phosphorus intake for persons in the highest quartile of phosphorus intake was slightly less than 2000 mg/d: a calculation based on these figures (not provided in the paper) shows that an increase in intake from 1400 to 2000 mg/d could be expected to increase the associated risk of mortality by approximately one-third. Higher dietary phosphorus density was also associated with a higher all-cause mortality rate, as well as with a higher death rate from CVD. The study in persons with moderate CKD, did not find an association between higher dietary phosphorus intake and death in early-stage III CKD (Murtaugh and others 2012).

One study investigated associations between dietary phosphorus intake and evolution of "multimorbidity" (anemia, hypertension, hypercholesterolemia, diabetes, arthritis, hepatitis, CHD, asthma, stroke, fracture, and cancer) (Ruel and others 2014). Higher dietary phosphorus intakes were associated with lower morbidity progression.

Two studies investigated associations between dietary phosphorus intake and physical performance in older adults. In one of these studies, a quarter of the subjects had phosphorus intakes below 105% of the RDA, and higher intakes were associated with better performance (lower extremity performance) (Sharkey and others 2003). In the other study, higher phosphorus intake was not associated with a change in muscle strength (although it was associated with an increase in aLM) (Scott and others 2010).

A study reported that girls with phosphorus intake greater than 647 mg/d had an earlier menarche than girls with lower intakes (Ramezani Tehrani and others 2013). The authors stated that earlier menarche is a risk factor for several diseases in later life and for all-cause mortality.

Although several of these studies were large and well designed, all were observational. Their diversity, their small number, and, in some cases, the difficulty in resolving apparently contradictory findings from related studies (discussed in some of the reports, for example, Tavani and others 2005) preclude drawing general conclusions about possible associations of food-additive phosphates or total dietary intake of phosphorus with morbidity or mortality. Assessing net effects of possible positive and negative associations across clinical areas is not possible.

The different ranges of phosphorus intake examined and the relationship of these ranges to dietary reference intakes and *de facto* population distributions of dietary phosphorus intakes complicate interpretation, even within circumscribed health areas. One of the studies in adult populations not selected for compromised renal function used a dietary phosphorus intake of 1119 mg/d to delimit or otherwise define the subject category with the highest intake (Ruel and others 2014), while another used 2091 mg/d (Chan and others 2000). Values used to delimit categories with the lowest intakes varied between 951 and 1655 mg/d across studies (Boutron and others 1996; Chan and others 2000). Differences between the high and low category limits in each study varied between 132 and 797 mg/d (Boutron and others 1996; Ruel and others 2014). In the 6 reports of prostate cancer studies containing the data needed to make the comparison, values used to delimit the highest category ranged from 1434 to 2091 mg/d (Chan and others 2000; Kesse and others 2006); values used to delimit the lowest category ranged from 984 to 1655 mg/d (Chan and others 2000; Merritt and others 2015); and within-study category differences ranged from 267 to 704 mg/d (Kesse and others 2006; Wilson and others 2015). These limits are displayed in Table 10.

A context for these figures is provided by the dietary reference intakes set by the U.S. Inst. of Medicine (IOM): the RDA for men and women aged 19 y and older was set at 700 mg/d, with a tolerable upper intake level between 3000 and 4000 mg/d, depending on age, pregnancy, and lactation (Otten and others 2006). The average (standard error [SE]) intake of phosphorus in U.S. persons aged 20 y and older is 1418 (13) mg/d (National Health and Nutrition Examination Survey (b)). The study by Chang and others (2014) showed an increasing HR for all-cause mortality, starting at an intake of 1400 mg/d. The study reported by Sharkey

Table 10–Values used to delimit or otherwise define categories of phosphorus intake

Parameter	Lowest category	Highest category	Within-study difference (highest compared with lowest category)
All studies with required data[a]			
Cross-study maximum (mg/d)	1655	2091	797
Cross-study minimum (mg/d)	951	1119	132
All prostate cancer studies with required data[b]			
Cross-study maximum (mg/d)	1655	2091	704
Cross-study minimum (mg/d)	984	1434	267

[a] 12 publications included the required data.
[b] 6 publications included the required data.

and others (2003) is notable for including a population of subjects (homebound elderly), of whom 26% had diets containing less than 105% of the RDA for phosphorus.

The many methods used to acquire raw dietary data, the many assumptions made in calculating uncorrected phosphorus intakes from the raw data, the adjustments made to correct these data, and the many covariates introduced into the statistical analyses subsequently employed to arrive at conclusions differ significantly from study to study. These are listed by study in Table 9, and many of these features limit the utility of the data produced by the studies possessing them. The difficulty of distinguishing associations of phosphorus itself from associations of the foodstuffs ingested and associations of conutrients, especially calcium, is apparent in most of the reports reviewed in this section (for example, the discussion in Merritt and others 2015). Not all substances coingested with phosphorus could be examined for independent association with the outcome being investigated; one report, among many others, that discusses this point is the report by Chan and others (1998). Derived outcome scores (for example, the paper by Sharkey and others 2003) and sophisticated statistical techniques are used in some analyses. The limitations of the studies are emphasized within the discussion sections of the reports, and most qualify their conclusions heavily and limit their recommendations to the need to perform additional studies, especially randomized, controlled trials. Among the partial exceptions to this generalization is the report by Chang and others (2014), who reported an association between increased dietary phosphorus intake and all-cause mortality in a subject sample representative of the U.S. population. These authors stated that "[their] findings may have important public health implications." Further discussion of the methodological difficulties apparent in these reports is provided in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

All the studies discussed in this section were observational. The quality of evidence from these studies is considered low, based on the criteria used for rating the quality of studies described in Appendix C.

Other associations and analyses

Load of ingested phosphorus. A total of 11 primary publications assessed the effects of load of ingested phosphorus. Phosphorus load was controlled by intravenous administration (Ito and others 2007), oral supplementation (Galloway and others 1996; Kärkkäinen and Lamberg-Allardt 1996; Grimm and others 2001; Zorbas and others 2002; Ditscheid and others 2005; Kakuris and others 2007; Shuto and others 2009; Karp and others 2013), or short-term diet modification (Burnett and others 2006; Goto and others 2014).

One primary publication assessed the effects of intravenously administered phosphorus in healthy men. Ito and others (2007) conducted a phosphate-infusion study in 4 healthy males to determine the short-term association of elevated serum phosphate with FGF-23 concentrations. After overnight fasting, 4 healthy males were intravenously administered dibasic potassium phosphate dissolved in saline at 10 mEq/h for 4 h. Blood samples were collected before infusion and hourly after the start of infusion for 6 h. Serum albumin, calcium, potassium, and phosphate were measured by an autoanalyzer. Serum phosphate was 3.23 ± 0.21 mg/dL at baseline, 6.00 ± 1.08 mg/dL at 3 h ($P < 0.05$ compared with baseline), and 5.80 ± 0.79 mg/dL at 4 h ($P < 0.05$ compared with baseline). After infusion, serum phosphate gradually decreased to 3.68 ± 0.62 mg/dL at 6 h. Phosphate infusion decreased serum calcium: $96.7\% \pm 0.4\%$ of baseline at 2 h and $94.2\% \pm 1.0\%$ of baseline at 4 h. Phosphate infusion increased serum PTH levels: iPTH was $153.9\% \pm 16.5\%$ of baseline at 2 h and $205.0\% \pm 24.1\%$ of baseline at 4 h. Administration of intravenous phosphorus resulted in no changes in FGF-23 concentrations.

Three primary publications assessed the effects of supplemented phosphorus in healthy women (Kärkkäinen and Lamberg-Allardt 1996; Grimm and others 2001; Karp and others 2013).

Karp and others (2013) conducted a short-term intervention study to determine the effects of monophosphate and polyphosphate salts on markers of calcium and phosphorus metabolism in young women. A total of 14 healthy women aged 19 to 31 y were randomized into 3 controlled, 24-h study sessions. During each session, subjects received 3 doses of monophosphate, polyphosphate, or a placebo with meals in a randomized order. Meals for each session were identical. Both phosphate salts provided 1500 mg phosphorus per day. During both phosphate salt sessions, there was an increase in serum phosphate ($P = 0.0001$), urinary phosphate ($P = 0.0001$), and serum PTH (monophosphate, $P = 0.048$; polyphosphate, $P = 0.012$) as compared with levels associated with placebo. Ingestion of polyphosphate salts had a greater effect on diminishing urinary calcium than did monophosphate salts ($P = 0.014$). Results from this study suggest that polyphosphate salts bind to calcium more effectively than monophosphate salts in the small intestine.

Grimm and others (2001) conducted a phosphate-loading study in 10 healthy women aged 23 to 29 y. The study was divided into 3 periods:

- A commercial basic diet containing 1700 mg phosphorus and 1500 mg calcium per day for 4 wk.
- A supplemented diet containing 3008 mg phosphorus and 1995 mg calcium per day for 6 wk. (Phosphorus was supplemented with phosphorus-enriched orange juice [975 mg per

750-mL bottle] and 4 NaH_2PO_4 tablets containing 620 mg of phosphorus.)
- A commercial basic diet containing 1700 mg phosphorus and 1500 mg calcium per day for 4 wk (washout period).

Blood samples were collected at the beginning of the study, at the end of each study period, and in the middle of the supplementation period. Throughout the phosphorus supplementation period, all subjects reported intestinal distress. There were no changes in serum levels of calcium, phosphate, or zinc. There were no statistically significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption, and renal function during the phosphorus-supplemented period (Grimm and others 2001).

Kärkkäinen and Lamberg-Allardt (1996) conducted single and multiple oral phosphate dose studies to evaluate the effect of phosphate on calcium and bone metabolism in a randomized, controlled trial. Ten healthy female subjects were given 1500 mg of phosphorus in water or plain water as a single dose in a randomized order at 2 sessions. In the multiple-dose part of the study, 10 healthy female subjects were given three 500-mg doses in water or plain water in a randomized order. Calcium and bone metabolism markers were measured for 24 h. After phosphorus supplementation, when compared with placebo, serum phosphorus levels increased (single-dose study, $P = 0.00005$; multiple-dose study, $P = 0.0005$), serum calcium decreased in the single-dose study ($P = 0.0014$), urinary calcium excretion decreased (single-dose study, $P = 0.02$; multiple-dose study, $P = 0.013$), and the PTH concentration increased (single-dose study, $P = 0.0083$; multiple-dose study, $P = 0.014$). Markers of bone formation were also measured. Propeptide of type I collagen decreased in the single-dose study ($P = 0.04$) and BALP decreased in the single-dose study ($P = 0.027$) and multiple-dose study ($P = 0.026$). There was no significant change in osteocalcin in either study (Kärkkäinen and Lamberg-Allardt 1996).

Four primary publications assessed the effects of supplemented phosphorus in active healthy males (Galloway and others 1996; Zorbas and others 2002; Kakuris and others 2007; Shuto and others 2009). Galloway and others (1996) studied the effects of short-term phosphate supplementation on the physical performance of 12 healthy male subjects of different aerobic fitness levels. A total of 6 trained cyclists (high-fitness group) and 6 untrained subjects (low-fitness group) performed a 20-min cycle ergometer exercise test at 70% of maximum oxygen consumption, followed by a 30-min rest period, then an incremental ride to exhaustion at 2 visits, 1 wk apart. Subjects consumed a drink with either 22.2 g dibasic calcium phosphate (treatment) or calcium carbonate (placebo) 90 min before exercise. Blood was drawn before treatment, during submaximal exercise, during recovery, and at exhaustion. Additionally, cardiorespiratory variables were measured during exercise. While the low-fitness group tended to have a higher plasma phosphate concentration before treatment, no treatment effects on plasma phosphate were noted in either group. Cardiorespiratory variables were significantly higher, as indicated by significantly higher performance in the high-fitness group than in the low-fitness group; however, these differences were a result of better fitness, and were not a result of phosphorus supplementation. Overall, short-term dibasic calcium phosphate supplementation did not affect aerobic performance. In addition, aerobic fitness level had no effect on the response to phosphate supplementation.

Zorbas and others (2002) determined the ability of healthy male subjects to retain phosphorus during prolonged periods of physical rest. All subjects had trained as long-distance runners and ran an average of 11.3 km/d. Freely ambulatory subjects made no changes to their training regimen or daily activities. For subjects randomized to the hypokinetic group, muscular activity was restricted to an average walking distance of 0.7 km/d for 364 d. Phosphorus-loaded subjects were administered a dose of 85.0 mg phosphorus per kilogram of body weight on days 1, 15, and 30 during the 30-d baseline period and every 60 d during the hypokinetic period. Phosphate loads were given as calcium phosphate. Subjects were randomized into 4 groups: (1) active unsupplemented control subjects, (2) unsupplemented hypokinetic subjects, (3) active supplemented control subjects, and (4) supplemented hypokinetic subjects. Urinary calcium and phosphorus loss, fecal phosphorus loss, serum phosphate, and serum calcium levels increased significantly ($P \leq 0.05$) in the supplemented hypokinetic group compared with the supplemented active group and in the unsupplemented hypokinetic group compared with the unsupplemented active group.

In a study similar to the one by Zorbas and others (2002), Kakuris and others (2007) determined the effects of phosphorus supplementation on phosphate balance during prolonged periods of physical rest. All subjects were students and ran an average of 9.5 ± 1.2 km/d. Ambulatory subjects made no changes to their training regimen or daily activities. For subjects randomized to the hypokinetic group, muscular activity was restricted to an average walking distance of 0.9 ± 0.1 km/d for 364 d. Phosphorus-loaded subjects were administered a dose of 0.7 mmol phosphorus per kilogram body weight during the pre-experimental and hypokinetic periods. Phosphate loads were given as dicalcium phosphate. Subjects were randomized into 4 groups: (1) active unsupplemented control subjects, (2) unsupplemented hypokinetic subjects, (3) active supplemented control subjects, and (4) supplemented hypokinetic subjects. Phosphorus imbalance, serum phosphorus and calcium levels, fecal phosphorus loss, and urine calcium and phosphorus loss increased in the supplemented hypokinetic group when compared with the supplemented active group and in the unsupplemented hypokinetic group compared with the unsupplemented active group. Overall, the authors suggested that during hypokinesia, phosphate imbalance resulted from the inability of the body to use phosphorus.

A double-blind crossover study evaluated the effect of dietary phosphorus loading on endothelial function in 11 healthy men (age: 21 to 33 y) (Shuto and others 2009). The subjects were alternately served breakfast meals containing 400 mg (steamed rice, boiled egg, ham, and milk [690 kcal, 110 g carbohydrate, 23 g protein, 16 g fat, 400 mg phosphorus, and 200 mg Ca]) or 1200 mg of phosphorus and a standard dinner (consisting of steamed rice, boiled egg, ham, and milk [690 kcal, 110 g carbohydrate, 23 g protein, 16 g fat, 400 mg P, and 200 mg Ca] with 800 mg P supplement dissolved in 22 mL of water). Meals were consumed over a period of 7 to 14 min. Serum phosphorus was measured over 8 h after the meals; peak concentrations occurred at 6 h for the 400 mg diet (3.9 ± 0.12 mg/dL), and at 2 h for the 1200 mg diet (5.0 ± 0.11 mg/dL). The serum phosphorus levels after ingestion exceeded the normal range (that is, were >4.5 mg/dL) in 8 of 11 subjects after the 1200 mg diet, while the serum phosphorus levels did not change significantly with the 400 mg meal (3.66 ± 0.2 mg/dL) and stayed within the normal range (2.5 to 4.5 mg/dL). Serum glucose levels at 2 h after the meals were not significantly different after either meal. Serum iPTH levels tended to decrease after breakfast, but were significantly higher after the 1200 mg meal than after the 400 mg meal. Other

serum chemistry measurements were not significantly different between the 2 meals. The effect of dietary phosphorus loading on endothelium-dependent vasodilation was evaluated by assessing postprandial changes in the %FMD. There was a significant decrease in %FMD 2 h after the 1200 mg meal, with a significant negative correlation between serum phosphorus levels and %FMD (Spearman's coefficient $r = -0.42$; $P = 0.006$) that normalized after at least 24 h. No significant correlation between serum phosphorus level and %FMD was observed after the 400 mg meal. The authors posited that these results demonstrated that dietary phosphorus loading may be involved in the postprandial elevation of serum phosphorus levels and that the short-term exposure to load of phosphorus was enough to decrease endothelium-dependent vasodilation, which can contribute to CVD.

In a placebo-controlled, double-blind, crossover study with pentacalcium hydroxytriphosphate supplementation, Ditscheid and others (2005) measured the ability of calcium phosphate to affect cholesterol metabolism in 31 healthy subjects. Pentacalcium hydroxytriphosphate was incorporated into bread; daily consumption of 140 g of pentacalcium hydroxytriphosphate-supplemented bread provided an additional 1060 mg calcium and 490 mg phosphorus compared when with unsupplemented placebo bread. Each crossover period lasted 4 wk. In week 4 of each period, subjects consumed a defined diet. Serum cholesterol concentrations decreased significantly ($P = 0.008$) after 4 wk of supplementation (4.36 mmol/L) when compared with placebo (4.60 mmol/L). There was no difference in excretion of total neutral sterols. However, during pentacalcium hydroxytriphosphate supplementation, the excretion of cholesterol increased ($P = 0.025$), while excretion of the cholesterol metabolite coprostanol decreased ($P = 0.025$). Bile acid excretion increased during pentacalcium hydroxytriphosphate supplementation ($P = 0.003$). Overall, pentacalcium hydroxytriphosphate supplementation significantly diminished serum cholesterol concentrations.

FGF-23 plays an important role in phosphorus metabolism, as discussed in Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes". Goto and others (2014) determined the effects of a standard low-protein diet on serum FGF-23, intact PTH, and $1,25(OH)_2D$ in patients with early (15 subjects) and advanced (20 subjects) CKD. Early CKD was defined as an eGFR greater than or equal to 60 mL/min/1.73 m^2 and proteinuria or hematuria for at least 3 mo; advanced CKD was defined as an eGFR less than 30 mL/min/1.73 m^2 for at least 3 mo. The effects of a standard low protein diet in subjects with advanced CKD are discussed in Appendix A1.2.1. All participants consumed a regular diet (15 to 20 mg/kg/d of phosphorus) for 2 d, followed by a low-protein diet (10 to 15 mg/kg/d of phosphorus) for 4 to 6 d. Fasting blood samples and 24-h urine samples were collected on the final day of each diet regimen. A total of 35 subjects were included in the final analysis. None of the subjects in the early CKD group had diabetes. Serum FGF-23 levels significantly decreased after the low-protein diet regimen (in early CKD, from 52.8 to 38.6 pg/mL; $P = 0.006$). There was no significant change in serum PTH in the early CKD group. Serum $1,25(OH)_2D$ significantly increased in the early CKD group (36.0 to 47.0 pg/mL; $P = 0.03$). Serum calcium levels were unchanged. Urinary phosphorus levels significantly decreased. Overall, short-term consumption of a low-protein diet decreased serum FGF-23 levels and increased serum $1,25(OH)_2D$ levels in subjects with early CKD.

Proteins are a major source of dietary phosphorus. In a randomized, controlled trial, Burnett and others (2006) examined the role of dietary phosphate in regulation of FGF-23: effects on serum phosphorus concentration were also examined. The study randomized 66 healthy subjects (28 males, 38 females; aged: 18 to 45 y), based on sex, to either a phosphate-depleted diet (500 mg/d) or to a phosphate-loaded diet (2500 mg/d) for 5 d after a 4-d run-in diet (900 mg/d). Subjects only consumed food and beverages during the study that was prepared by the General Clinical Research Center dietitians. During the 1st 4 d of the trial, subjects consumed a run-in diet that contained 900 mg of phosphate daily. During the last 5 d of the study, the phosphate-depleted group consumed 500 mg of phosphate daily plus aluminum and magnesium hydroxide to bind dietary phosphate, whereas the phosphate-loaded group consumed 2500 mg of phosphate daily. On days 1 through 4, the diet contained approximately 380 g of carbohydrate, 76 g of fat, 77 g of protein, 1000 mg of calcium, 900 mg of phosphate, and 3300 mg of sodium. On days 5 through 9, the protein content was decreased for both groups to facilitate the decrease in dietary phosphate in the phosphate-depleted group. Starting on day 5, the phosphate-depleted group received 2.2 g of aluminum and magnesium hydroxide 4 times a day with meals to decrease absorption of dietary phosphate, and the phosphate-loaded group received phosphate supplements (either Neutra-Phos or Phos-NaK) 4 times a day with meals such that the total daily phosphate intake was 2500 mg (500 mg from the diet and 2000 mg from the supplements). Dietary phosphate loading had no effect on serum phosphate concentrations. When compared with male subjects, female subjects in the phosphate-loading group had significantly higher levels of phosphate on day 9 only (3.7 ± 0.4 mg/dL compared with 3.1 ± 0.5 mg/dL; $P = 0.01$). Phosphate deprivation decreased serum phosphate levels: mean serum phosphate levels decreased from 3.2 ± 0.5 to 2.8 ± 0.6 mg/dL ($P < 0.01$). There was no difference between male and female subjects in the phosphate-depleted group ($P = 0.64$ to 0.90). In this study, dietary phosphate deprivation reduced serum phosphate levels, but dietary phosphate loading had no effect on serum phosphate.

A summary of studies that evaluated the associations of consumption of load of phosphorus is presented in Table 11. In addition, studies that evaluated the association of load of phosphorus with regulatory hormones and physiological outcomes are described in Section "Association of phosphorus load with regulatory hormones and other physiological outcomes". The results from studies that evaluated the associations of load of phosphorus were highly variable. In studies that measured serum phosphorus after short-term phosphorus supplementation, a number of acute changes in serum phosphorus levels and physiological measures were observed (Kärkkäinen and Lamberg-Allardt 1996; Kemi and others 2006; Karp and other 2013). In most studies, serum phosphorus levels increased after acute exposures to load of phosphorus in healthy individuals. However, the studies only evaluate acute changes, and the long-term consequences of these changes were not evaluated. In contrast, Galloway and others (1996) reported no effect on serum phosphorus levels or aerobic fitness after acute phosphorus supplementation. Additionally, Grimm and others (2001) measured serum phosphorus levels at 3 and 6 wk during a 6-wk course of phosphorus supplementation; they reported no change in serum phosphorus levels. During extended periods of hypokinesis, serum phosphorus levels were shown to be increased (Zorbas and others 2002; Kakuris and others 2007). In healthy individuals, dietary phosphate loading had no effect on serum phosphate concentrations, but phosphate deprivation decreased serum phosphate levels (Burnett and others 2006). One study determined that calcium phosphate supplementation increased bile

Table 11–Summary of clinical studies evaluating phosphorus load

Study reference	Study population	Description of phosphorus load	Variables	Duration of exposure to phosphorus load	Outcome
Ito and others (2007)	4 healthy men	Dibasic potassium phosphate dissolved in saline, infused at a rate of 10 mEq/h for 4 h	Serum phosphorus, FGF-23, PTH	4-h infusion, monitor serum levels for 6 h	Increased serum PTH, no change in FGF-23.
Karp and others (2013)	14 healthy females, age 19 to 31 y	3 doses each of monophosphates (MPs) and polyphosphates (PPs) provided 1500 mg phosphate/d or placebo	Urinary phosphate, and serum PTH, phosphorus	3 doses with meals during 24-h period	MP and PP increased serum phosphate, urinary phosphate, and serum PTH PP decreased urinary calcium excretion more than MPs.
Shuto and others (2009)	11 healthy men, age 21 to 33 y	Meals contained 400 mg or 1200 mg phosphorus	% Flow-mediated dilation of the brachial artery before and 2 h after the meals	One meal; 7 to 14 min duration	Increased serum phosphorus at 2 h and significantly decreased flow-mediated dilation of brachial artery. Serum PTH higher after the 1200-mg P meal than after the 400-mg P meal.
Grimm and others (2001)	10 healthy women age 23 to 29 y	Control Period 1: Basic diet of 1700 mg P and 1500 mg Ca per day for 4 wk Supplement Period: Basic diet with 1700 mg P and 1500 mg Ca per day for 4 wk Period 2: Supplemented diet with 3008 mg P and 1995 mg Ca per day for 6 wk Control Period 2: Basic diet of 1700 mg P and 1500 mg Ca per day for 4 wk Period 3: 4 wk washout period	Serum phosphorus, calcium, bone-related hormones, pyridinium crosslinks as markers of bone resorption and renal function	Basic diet: 4 wk. Supplemented diet: 6 wk	No significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption and parameters of renal function were identified.
Kärkkäinen and Lamberg-Allardt (1996)	10 healthy females	Part 1: single dose of 1500 mg Pi in water, or placebo Part 2: 3 doses of Pi (500 mg each) in water, or placebo	Serum phosphorus, PTH, calcium and bone metabolism, BALP activity, serum osteocalcin	Single-dose exposures	Serum phosphate increased, serum calcium decreased, serum PTH increased, serum BAL increased, no change in osteocalcin.
Galloway and others (1996)	12 healthy male subjects	Dibasic calcium phosphate or calcium carbonate (placebo) beverage	Aerobic fitness (VO_2 max), blood 2,3-DPG, plasma lactate, oxygen uptake, oxygen pulse, minute ventilation, time to exhaustion	Single-dose exposures of calcium phosphate-supplemented beverage	Phosphate ingestion has no effects on measures of aerobic fitness.
Zorbas and others (2002)	40 male athletes	Calcium phosphate, 85-mg/kg load	Urinary calcium and phosphorus, serum phosphate, and serum calcium levels	Day 1, 15, and 30 and every 60 d	Urinary calcium and phosphorus loss, fecal phosphorus loss, serum phosphate, and serum calcium levels increased significantly in hypokinetic subjects compared with active group.
Kakuris and others (2007)	40 healthy male subjects 24.2 ± 2.0 y	0.6 mmol/kg dicalcium-phosphate	Phosphorus balance, serum phosphorus and calcium, fecal and urine calcium and phosphorus	364 d	During hypokinesia, Pi imbalance, serum phosphorus and calcium levels, fecal phosphorus loss, and urine calcium and phosphorus loss increased in hypokinetic subjects.
Ditscheid and others (2005)	31 young healthy adults, age 25 ± 2 y	Amorphous calcium phosphate incorporated into bread; 1060 mg calcium and 490 mg phosphorus added to 140 g bread	Serum cholesterol concentrations (LDL, HDL)	4 wk	Serum cholesterol concentrations were lower after 4 wk of supplementation with calcium phosphate bread ($P = 0.008$). Serum LDL and LDL:HDL ratio lower with CaP bread.
Goto and others (2014)	15 early, 20 advanced CKD patients	Regular diet 15 to 20 mg/kg/d phosphorus; low protein diet 10 to 15 mg/kg/d phosphorus	Serum FGF-23, PTH, and $1,25(OH)_2D$	Regular diet: 2 d. Low protein: 4 to 6 d	Low P diet decreased serum FGF-23 levels, increased $1,25(OH)_2D$. Changes in FGF-23 levels correlated with changes in 24 h urinary phosphorus excretion in the advanced CKD group.
Burnett and others (2006)	66 healthy adults, 18 to 45 y	Phosphorus-depleted diet: 500 mg/d Phosphorus-loaded diet: 2,500 mg/d	Serum FGF-23 concentrations	5 d after 4-d run-in diet of phosphorus 900 mg/d	Phosphorus depletion: decreased serum FGF-23 and phosphorus concentrations. Phosphorus load: not enough evidence to determine the effects of phosphate loading on serum phosphate levels.

$1,25(OH)_2D$, 1,25 dihydroxyvitamin D; BALP, bone-specific alkaline phosphatase activity; Ca, calcium; CKD, chronic kidney disease; FGF-23, fibroblast growth factor 23; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MP, monophosphate; P, phosphorus; Pi, inorganic phosphorus; PP, polyphosphates; PTH, parathyroid hormone; VO_2max, maximum oxygen consumption.

acid excretion, which resulted in a decrease in serum cholesterol (Ditscheid and others 2005). Short-term consumption of a low-protein, low-phosphate content diet resulted in decreased serum FGF-23 and increased serum 1,25D concentrations in subjects with early CKD (Goto and others 2014). Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake included the limited ability of the outcomes of phosphorus-intake manipulation through the administration of phosphorus supplements (or the implementation of other short-term dietary alterations) to draw conclusions about the effects of habitual diets; and the limited ability of the outcomes examined in these studies to serve as surrogates for morbidity and mortality. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Phosphorus content in food. Several studies evaluated intrinsic dietary and AP, but few described the methods used to measure the content of phosphorus or described the type of phosphorus content in foods that were evaluated in the studies. This section summarizes the methods used to evaluate the phosphorus contents in meals.

Several methods are available to assess the daily dietary intake of phosphorus. These are thought to be equally accurate and reliable. However, there are many well-recognized difficulties and limitations in adequately quantifying dietary intake of food-additive phosphate and organic phosphate; these limitations are discussed briefly in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies", and the "Methods" include the following:

- Duplicate portion sampling and spectrophotometric phosphorus analysis
- Duplicate portion sampling and food composition tables
- 24-h dietary recall and food composition tables

A total of 108 different complete hospital meals were sampled daily for 36 consecutive days in southeast Spain (Navarro-Alarcon and others 2012). Duplicates of all meals consumed during each 24-h period were collected. Each meal was recorded, weighed, and processed for analysis. The mean daily dietary phosphorus intake determined by spectrophotometry was 1106.4 ± 221 mg/d, which was significantly lower ($P < 0.001$) than that estimated from food composition tables (1480 ± 221 mg/d for duplicate portion sampling and 1515 ± 222.7 mg/d for 24-h dietary recall). In this study, the food composition tables overestimated the phosphorus content of the meals analyzed. This could be attributed to differences in the composition of meals caused by food variability, geographic location, technological and cooking processes, and the overestimation of phosphorus additives.

Welch and others used standardized 24-h dietary recall software to determine the variation in mineral intake across European countries participating in the EPIC study (Welch and others 2009). The EPIC study is a prospective cohort study conducted in 10 Western European countries: Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, the Netherlands, and the U.K. A total of 36034 subjects were included in this analysis (8% of the EPIC population), aged 35 to 74 y. Overall, women had significantly lower intakes of all nutrients than did men ($P < 0.001$). In men, phosphorus intake ranged from 1425 mg/d in the U.K. to 2070 mg/d in Greece, a difference of 45%. In women, phosphorus intake ranged from 1089 mg/d in Ragusa, Italy, to 1478 mg/d in Aarhus, Denmark, a difference of 36%. There were significant decreases in phosphorus intake as age increased in Spain, Italy, the U.K., Sweden, and north and east Norway. Dairy foods and products, cereals and cereal products, and meats and meat products contributed to 63% to 75% of phosphorus intake in all countries. Alcoholic beverages contributed to 9.2% of phosphorus intake in men in Germany, 6.1% in the Netherlands, and 5.0% in Italy. In women, the phosphorus contribution from alcoholic beverages was less than 3%.

An analysis examined the potassium and phosphorus contents in a variety of enhanced and regular meat and poultry products that are available in local retail stores in New Jersey (Sherman and Mehta 2009). Measurement of phosphorus content was based on the Association of Analytical Communities "Official Method 984.27" using atomic spectroscopy procedures. Meat or poultry products were considered "enhanced" when this word was used on the package label, or when other terms suggesting the presence of food additives were noted on the label such as "cured," "contains solution," and "natural flavorings." Other meat and poultry products were considered "regular" (or additive-free) if there was no evidence indicating the presence of food additives. Phosphorus content was measured from uncooked meat and poultry items and was reported as milligrams per 100 g (mg/100 g) of product or as milligrams per gram (mg/g) of protein. Enhanced meat and poultry products had an average phosphorus-to-protein ratio that was 28.4% greater than the ratio for regular products that were not enhanced. The phosphorus content in enhanced meat and poultry products that did not contain specific information on the product label was found to be highly variable, ranging from 6.86 to 17.35 mg/g protein. The authors concluded that uncooked meat and poultry products that are enhanced may contain additives that increase phosphorus content by as much as 2-fold and that the modifications may not be discernible from the food label.

A study compared the measured phosphorus content of a number of chicken products with the amount estimated from a reference source that dietitians use to advise patients (Sullivan and others 2007). Thirty-eight chicken samples from a variety of store types, products, and brands were purchased. The chicken products were prepared according to package directions and were cooked at 350 °F until they reached an internal temperature of 165 °F. Samples were shipped to Medallion Laboratories to measure phosphorus content in each sample. The expected phosphorus content of each chicken product was determined by ESHA Food Processor SQL Software (Version, 9.8). Of the 38 chicken products, 35 (92%) had phosphorus-containing additives listed among their ingredients. Additives included sodium phosphate (present in 71% of products), sodium aluminum phosphate (32%), sodium acid pyrophosphate (26%), monocalcium phosphate (26%), and sodium tripolyphosphate (16%). Ten products contained 2 additives, and another 10 products contained 3 additives. The actual phosphorus content from boneless chicken breasts was somewhat less than the content expected from the nutrient database, while the actual phosphorus content was greater than the content expected from the nutrient database for other chicken products. The actual phosphorus content exceeded expected phosphorus content by an average of 84 mg/100 g for breaded breast strips. Of note, there was significant variability of phosphorus content for different chicken products.

The difference between actual and expected phosphorus content was significantly higher for products containing phosphorus additives than for products without additives (−38 compared with +68 mg/100 g, $P < 0.0001$). Two 100-g servings of

additive-containing products would provide an average of 440 mg of phosphorus (range: 256 to 634 mg), which the authors noted would constitute about half the total daily recommended intake for dialysis patients. The authors concluded that phosphorus-containing additives are present in the vast majority of chicken and significantly increase the amount of phosphorus in chicken products. Available reference sources do not reflect this higher phosphorus content, and the variation between similar products makes it impossible for patients and dietitians to accurately estimate phosphorus content.

The estimated dietary intake of calcium, magnesium, and phosphorus in 112 elderly institutionalized subjects in Spain (87 females and 25 males, mean age of 83 ± 7 y) was determined using duplicate diet sampling to establish any related difference with the results obtained using food composition tables (Moreno-Torres and others 2001). Food intake was determined by the weighed food record method over 7 d. Transformation of food into energy and nutrients was determined by a computer program based on Wander's food composition table that includes the Spanish food composition tables' paired food samplings (duplicate diet technique) of all foods and beverages. The estimates based on food composition tables were higher than the values measured by direct chemical analyses: calcium, 6.7% to 9.5%; magnesium, 26.9% to 33.l%; and phosphorus, 16.9% to 27.0%. ANOVA (paired samples) showed significant differences ($P < 0.05$) in all the minerals analyzed. The authors concluded that these results suggest that the use of food composition tables overestimates the calcium, magnesium, and phosphorus intakes in nutritional trials.

A study examined the accuracy of food composition table-based estimation of dietary nutrient element intake compared with analytical measurement of the quantity of the nutrient element (Zhang and others 1999). In the study, 884 samples of 24-h food duplicates were collected from adult women in 23 study sites from 6 areas in Asia. The quantity of phosphorus and other nutrient elements was estimated using FCTs established for the geographic areas, and nutrients were measured using inductively coupled plasma–mass spectrometry. The estimated amounts of phosphorus were generally greater than the measured amounts, with an estimated-to-measured ratio range of 113% for Japan to 306% for the Philippines. Statistical analyses revealed that the differences between pairs were significant ($P < 0.01$) in all areas. The authors concluded that the food composition table-based estimates of dietary intakes of phosphorus, as well as of calcium and iron, differed from the results of instrumental analyses of the elements.

Szajkowski determined the mineral intake of 24 children aged 9 to 14 y in an economically developed region of Poland using a questionnaire to document foods consumed during the previous 24 h (Szajkowski 1996). The same cohort of children answered the questionnaire during a week selected in each of the 4 seasons. Meals were then prepared and subjected to spectrophotometric phosphorus analysis. The Polish nutritional standards of 1994 recommend 900 mg/d of phosphorus for children aged 9 to 14 y. Based on Szajkowski's analysis, boys consumed 1032 mg/d of phosphorus and girls consumed 932 mg/d, thus exceeding the daily normal allowance of phosphorus.

Sugiyama and others (2009) determined the phosphorus intake of 90 children aged 3 to 5 y attending preschools in Japan. Duplicate portions of all food and drinks were collected for 3 d (1 d each in summer, autumn, and winter) for spectrophotometric phosphorus analysis. No significant differences were identified in phosphorus intake among the 3 age groups, but a sex difference was seen ($P < 0.05$). The median phosphorus intake was 754 mg/d for boys and 635 mg/d for girls. There was a significant age difference seen in the Ca:P ratio between children aged 3, 4, and 5 y (Ca:P was 0.639 ± 0.168, 0.635 ± 0.188, and 0.512 ± 0.165, respectively; $P < 0.05$). Additionally, there was a significant difference in daily phosphorus intake during each of the 3 seasons studied; median phosphorus intake was 718 mg/d in summer, 735 mg/d in autumn, and 497 mg/d in winter. Phosphorus intake was positively correlated with the following foods and beverages: milk and dairy products, meats, beans and bean products, green and yellow vegetables, hypochromic vegetables, fruits, sugars, and milk.

Data from 1992 subjects evaluated in the NHANES (2005 to 2006) observational cohort were analyzed to determine calcium and phosphorus intakes and the resulting Ca:P ratios (by mass) across sex and older adult age groups (Adatorwovor and others 2015). The results indicated lower intakes of calcium and higher intakes of phosphorus compared with the current RDAs. Women within the 50- to 70-y group and the >71-y age group had greater Ca:P intake ratio than men in the same age groups, due to higher consumption of calcium supplements and calcium-containing foods, and reduced consumption of phosphorus-containing foods compared with men. Ca:P intake ratios were lower in older men than in older women, possibly due to greater consumption of phosphorus-rich food in men.

In summary, Navarro-Alarcon and others (2012) showed that food composition tables overestimated the phosphorus content of the meals analyzed. The difference may have been attributed to differences in geographic location, technological, and cooking processes. The results from 2 studies indicated that dairy foods and products, meats, and cereal and cereal products were the principal sources of phosphorus intake in Western Europe and in Japan (Sugiyama and others 2009; Welch and others 2009). Additionally, Sugiyama and others (2009) reported seasonal variations in phosphorus intake that corresponded to the seasonal variations in food availability and preparation. Szajkowski and others (1996) reported that dietary phosphorus exceeded the daily normal allowance of phosphorus in Polish children aged 9 to 14 y. A study that compared nutritional components of diets in food composition tables with chemical analyses of nutrients demonstrated that the use of food composition tables overestimated the calcium, magnesium, and phosphorus intakes in nutritional trials (Moreno-Torres and others 2001). Two studies reported differences between measured quantities of phosphorus in food and the amounts of phosphorus described in FCT or in nutritional guides. One study that examined the accuracy of FCTs in Japan and the Philippines showed statistically significant differences between the quantities of phosphorus estimated using FCTs compared with amounts measured using plasma–mass spectrometry (Zhang and others 1999). The results demonstrated that FCT-based estimates of dietary intakes of phosphorus were greater than measured amounts of consumed phosphorus. Another study, which compared the measured amounts of phosphorus content in chicken products with quantities estimated from a reference source used by dieticians, revealed differences between the measured contents and phosphorus contents expected on the basis of nutritional reference sources (Sullivan and others 2007). The differences between measured and expected phosphorus contents were significantly greater for products containing food-additive phosphate than in products without food-additive phosphate. An additional study used atomic spectroscopy procedures to analyze the phosphorus content in a variety of "enhanced" and regular meat and poultry products available in the local retail stores in the United States (Sherman and Mehta 2009). Meat

or poultry products were considered "enhanced" when labels included the term "enhanced" or when language suggesting the presence of food additives, such as "cured," "contains solution," and "natural flavorings," was noted on the label. Greater quantities of phosphorus were found in enhanced meat and poultry products than in products that were not labeled as enhanced. Differences in dietary intakes of calcium and phosphorus were associated with different Ca:P intakes in older men and women (Adatorwovor and others 2015). Older women were noted to have greater Ca:P intake ratio than men of the same age group. This was attributed to greater intake of calcium supplements and calcium-containing foods, and lower consumption of phosphorus-containing foods.

Review articles, expert opinion, and commentary. Although no systematic literature search and selection were performed for publications other than primary research articles, many publications were encountered when preparing the white paper that integrated and commented on different parts of the diverse body of information available on relationships between dietary phosphorus and human health. These articles may be categorized as follows:

- Publications by authoritative bodies
- Academic review articles
- Authors' discussions in primary research publications
- Articles and information designed for and targeting the public at large

Publications by authoritative bodies and academic review articles were not systematically identified or reviewed. Publications in the 1st 3 categories are discussed briefly below: discussion of those in the last category is beyond the scope of this document.

Publications by authoritative bodies are cited elsewhere in the white paper. These include guidelines issued by IOM (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board - Inst. of Medicine 1997; Otten and others 2006) and by EFSA (European Food Safety Authority 2005, 2015) (for example, Sections "Introduction", "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies", and **"Summary of evidence: Total dietary phosphorus and clinical outcomes"**). IOM set ULs for dietary phosphorus intake that are considerably greater than the intakes of the vast majority of the U.S. population; at the same time, the IOM 2006 guidelines state the following:

Concern about high phosphorus intake has been raised because of a probable population-level increase in phosphorus intake through colas and a few other soft drinks that contain phosphoric acid and processed foods containing phosphate additives. However, further research is necessary in this area.

EFSA determined that there were insufficient data to establish an UL for dietary phosphorus intake. The EFSA guidelines include useful summaries of data from several countries in the European Union. In addition, at the request of the European Commission, EFSA produced a scientific assessment of concerns raised in a review article by Ritz and others (2012) (also alluded to below): EFSA concluded that the publications included in the review by Ritz were unable to support causal associations between serum phosphate concentration and the adverse effects observed in the studies they report, and did not allow evaluation of the specific role of phosphate food additives; the EFSA assessment states that EFSA will reevaluate the use of phosphates as food additives with high priority by December 31, 2018 (European Food Safety Authority 2013). A recent report prepared by the World Health Organization International Agency for Research on Cancer determined "sufficient evidence" of the carcinogenicity of processed meat, did not mention food additives or phosphate, and discussed the formation of N-nitroso-compounds during food processing (Bouvard and others 2015). These assessments will be published in volume 114 of the IARC Monographs.

A sample of 12 editorial or review articles is briefly discussed in this section. Nine of these had the general population (or subpopulations not defined by the presence of CKD) as their focus, and 3 focused on populations with CKD but recorded concerns also about potential risks of phosphorus intake in the general population. Four of the articles were published in an issue of Annals of the New York Academy of Sciences devoted to reporting proceedings of a 1-d symposium (entitled, "Current Dietary Phosphorus Intake: Are There Potential Implications for Public Health?") held in 2013 (Anderson 2013; Menon and Ix 2013; Uribarri 2013).

Most of the review articles are tentative in their conclusions and indicate awareness of possibly unwarranted extrapolation of findings from research studies they cite. Many highlight the paucity of, and the need for, interventional research studies, and the limitations of observational studies. Several have statements about increases over time in the exposure of many populations to total dietary phosphorus and to food-additive phosphate. Several recommend mandatory labeling of foods with information about phosphorus content and regulation of this content by responsible authorities. One publication specifically recommends a "proactive approach" by the food industry in this regard (Anderson 2013). Selected verbatim quotations from these reviews are presented in Table 12 to illustrate common themes as well as the range of conclusions reached by authors and the range of tones they employ: the last vary from the tempered (for example, the review by Menon and Ix 2013) to the seemingly biased, polemic, and propagandist (for example, the reviews by Ritz and others 2012 and Pizzorno 2014). It is notable that the dates of publication of the review articles suggest that the authors did not have data available to them that were not also available to EFSA (European Food Safety Authority 2015), which was unable to reach definitive conclusions about risks or safety of dietary phosphorus.

Repercussions of the tones used by authors and of the sometimes tendentious way they present the content of their articles and formulate their conclusions may be illustrated by one reaction to the review article by Ritz and others (2012). Ritz and others titled this article, "Phosphate Additives in Food—a Health Risk" and called for steps to be taken "to limit the damage done by this newly recognized cardiovascular risk factor" (Table 12). A stated purpose of Ritz and others in publishing the review article was "to acquaint laypersons interested in health policy with the problem of excessive phosphate intake." Specifically as a result of the publication of this article, the European Commission requested that EFSA to undertake a scientific assessment of the concerns it raised. EFSA conducted the assessment and issued its findings in a publication entitled "Assessment of one published review on health risks associated with phosphate additives in food." EFSA pointed out that the article does not report the outcome of a review that was systematic and that "other publications report findings that are inconsistent or conflict with [the] conclusions [drawn by Ritz and others 2012]": such publications are not discussed by Ritz and others in their review article.

Selected verbatim quotations from a sample of 12 primary research publications are presented in Table 13. The observations about review articles provided above in this section are largely applicable to these publications as well. Most of the publications call for further investigation, for example, one notes the need for

Table 12–Illustrative verbatim quotations from sample of review and editorial articles

First author, Year	Title	Focus[a]	Illustrative verbatim quotations
Uribarri, 2014	Dietary Phosphorus Intake and Health	General population	In summary, we believe the current study adds fuel to the premise that high dietary phosphorus intake is a risk factor for bone and CVD health, not just in CKD patients but also in the general population. The increased cumulative use of phosphorus ingredients in food processing clearly deserves further study in view of what is now being shown about the potential toxicity of excessive phosphorus intake. Further work is needed to define whether these associations represent real causality; however, in the meantime, we need to take some actions such as obligating food manufacturers to label the phosphorus content of their products on the required Nutrition Facts panel, which would enable consumers to determine their phosphorus intake. It is evident from the ever-increasing studies in the general population that the stakes are too high to simply ignore these associations.
Pizzorno, 2014	Canaries in the Phosphate-Toxicity Coal Mines	General population	Excessive phosphorus consumption has now been shown to be clearly associated with cardiovascular disease, osteoporosis, and all-cause mortality in the general, healthy population . . . . Cola drinks top the phosphate delivery hit list. Even disregarding the impact on blood sugar regulation and inflammation, cola drinks are in a class by themselves because of their total lack of potentially mitigating minerals (for example, calcium and magnesium) accompanying the hefty dose of phosphorus . . . . It is now known that the greatly increased risk of cardiovascular disease, bone loss, and all-cause mortality resulting from high phosphorus intake affects not only CKD patients, whose impaired renal function renders processed foods a source of phosphate toxicity, but also the general population with healthy kidneys . . . . Given that a direct relationship has now been established between high dietary phosphorus intake and all-cause mortality in healthy people, patients, particularly those with or at risk of cardiovascular disease or osteoporosis as well as those with or at risk of kidney disease or cancer, should be counseled to minimize consumption of processed foods, especially soft drinks. Current databases should be updated, and food manufacturers should be required to list the phosphorus content of processed foods on the nutrition facts panel.
Uribarri, 2013	Introduction to Dietary Phosphorus Excess and Health	General population	Should phosphorus be added to the list of nutrients recommended for reduced intake by the future 2015 Dietary Guidelines for Americans? The increased cumulative use of phosphorus ingredients in food processing merits further study, given what is now being revealed about the potential toxicity of phosphorus to heart, bone, and kidney when intake exceeds nutrient needs. The time has come to open the discussion that nephrologists and renal dietitians began about excess phosphorus intake to a discussion of its potential relevance to the general population.
Calvo, 2013	Public Health Impact of Dietary Phosphorus Excess on Bone and Cardiovascular Health in the General Population	General population	Although systematically underestimated in national surveys, phosphorus intake seemingly continues to increase as a result of the growing consumption of highly processed foods, especially restaurant meals, fast foods, and convenience foods. The increased cumulative use of ingredients containing phosphorus in food processing merits further study given what is now being shown about the potential toxicity of phosphorus intake when it exceeds nutrient needs . . . . Adverse health effects are beginning to emerge in individuals with normal renal function, which questions the safety of the high cumulative use of phosphate ingredients in processed and prepared foods. The increasing evidence of an association between high dietary intake and heart disease calls for a more thorough investigation of this issue.
Anderson, 2013	Potential Health Concerns of Dietary Phosphorus: Cancer, Obesity, and Hypertension	General population	Further investigation is needed to establish the significance of high-phosphate diets within a large segment of the U.S. population with normal renal function . . . . The food industry may also benefit from taking a proactive approach that results in a better health trajectory from reformulated products for the U.S. population and world markets.

CKD, chronic kidney disease; CVD, cardiovascular disease; U.S., United States.
[a] "General population" is used to indicate that an article focuses on the general population or on any subpopulation which does not have the presence of CKD as a defining characteristic.

(Continued)

Table 12–Continued

First author, Year	Title	Focus[a]	Illustrative verbatim quotations
Menon, 2013	Dietary Phosphorus, Serum Phosphorus, and Cardiovascular Disease	General population	However, outside the dialysis population, the links between dietary phosphorus intake and serum phosphorus concentrations, and dietary phosphorus intake and CVD events, are uncertain . . . . Therefore, before undertaking public health interventions that focus on dietary phosphorus restriction (or binder use) in the general population, high-quality evidence is called for that shows that changing dietary phosphorus impacts serum phosphorus as a surrogate outcome at a minimum and ultimately improves CVD risk (i.e., hard outcomes). Meanwhile, additional studies are required to identify nondietary factors influencing phosphorus concentrations and novel therapies that may provide more dramatic and sustained lowering of serum phosphorus concentrations.
Gutierrez, 2013	The Connection between Dietary Phosphorus, Cardiovascular Disease, and Mortality: Where We Stand and What We Need to Know	General population	In conclusion, given the central role of dietary phosphorus intake in the pathogenesis of disturbances of phosphorus homeostasis and the strong link between disordered phosphorus metabolism and cardiovascular disease, restriction of phosphorus consumption may represent an effective intervention for mitigating adverse cardiovascular outcomes in the general population. Although both experimental and human data support this possibility, the lack of reliable biomarkers of phosphorus intake and, by extension, the dearth of appropriate targets for gauging the efficacy of dietary phosphorus restriction beyond serum phosphorus concentrations complicate the design and initiation of clinical trials to test this possibility . . . . Given the markedly high phosphorus content of Westernized diets, these studies should be a high priority in future research.
Ritz, 2012	Phosphate Additives in Food—a Health Risk	General population	We believe that comprehensive public education, with a scientifically well-grounded explanation of the adverse effects of high phosphate intake along with easily understandable labeling of the phosphate content of food, could help considerably to limit the damage done by this newly recognized cardiovascular risk factor . . . . . Comprehensive labeling of phosphate additives in food—ideally, with a 'traffic-light' scheme—would also be desirable, as would a quantitative restriction of phosphate additives.
Kinney, 2002	Does Consumption of Cola Beverages Cause Bone Fractures in Children?	General population	"The adverse effect of carbonated soft drinks on bone health, whether by possible phosphoric acid- and caffeine related mechanisms in colas or by replacement of calcium-rich milk with soft drinks of any type, is of substantial public health concern, particularly for girls and women because of their proneness to osteoporosis in later life."
Uribarri, 2013	Dietary Phosphorus and Kidney Disease	CKD	What is needed now? It is clear that despite the large number of observational studies documenting an association between phosphorus and adverse outcomes, no randomized controlled interventional trials have compared high versus normal serum phosphate levels/dietary phosphorus intake on outcome . . . . If results turn out to be significant in dialysis patients, they could be extrapolated to the CKD and perhaps the general population.
Kalantar-Zadeh, 2010	Understanding Sources of Dietary Phosphorus in the Treatment of Patients with Chronic Kidney Disease	CKD	[CKD] affects 20 million Americans and is associated with high morbidity and mortality . . . . [phosphorus] is the main component of many preservatives and additive salts found in processed foods . . . . More accurate reporting of [phosphorus] content of foods by manufacturers, especially when mandated by the Food and Drug Administration, may result in improved public health nutrition and healthier control of dietary [phosphorus] intake with less risk for developing protein malnutrition in people with illnesses that render them more [phosphorus] intolerant . . . . Well-designed trials are needed to examine these hypotheses.
Noori, 2010a, 2010b	Organic and Inorganic Dietary Phosphorus and Its Management in Chronic Kidney Disease	CKD	Currently, there is no accurate or reproducible method to distinguish between protein-based organic and preservative- or additive-based inorganic phosphorus in the food . . . . The major public health implication from these considerations is that the phosphorus burden from inorganic phosphorus containing food additives is disproportionately high relative to organic phosphorus . . . . Hence, not only processed foods may contain a high amount of phosphorus in addition to the phosphorus naturally present in those foods, but also their phosphorus is more readily absorbed, because it is in an inorganic form . . . . More accurate reporting of phosphorus content of foods by manufacturers may result in improved public health nutrition and healthier control of dietary phosphorus intake with less risk of developing protein malnutrition in people with types of illnesses that render them more phosphorus intolerant.

CKD, chronic kidney disease; CVD, cardiovascular disease; U.S., United States.
[a]"General population" is used to indicate that an article focuses on the general population or on any subpopulation which does not have the presence of CKD as a defining characteristic.

Table 13–Illustrative verbatim quotations from sample of primary research articles

First author, Year	Title	Focus[a]	Illustrative Verbatim Quotations
Adatorwovor, 2015	Intakes of Calcium and Phosphorus and Calculated Calcium-to-Phosphorus Ratios of Older Adults: NHANES 2005 to 2006 Data	General population	"Prospective randomized controlled trials of experimental subjects fed diets containing different Ca:P ratios are needed to clarify the concerns about potential adverse skeletal effects and fractures resulting from the consumption of low Ca:P ratio diets. Additional research is needed to examine the relationship between Ca:P ratio and potential health effects on bone mineral density . . . . Dietary phosphorus (P) intakes, on the other hand, have been shown to greatly exceed current gender-specific RDAs. The intakes of P, however, may be even greater than reported because information on phosphorus food additives is not available to scientists or the public for use in generating total P amounts in the diet."
Chang, 2014	High Dietary Phosphorus Intake is Associated with All-Cause Mortality: Results from NHANES III	General population	"In conclusion, high phosphorus intake was associated with increased mortality in a nationally representative, healthy US population. Because of prevalence of high phosphorus intake in healthy adults and the widespread use of inorganic phosphorus additives in processed food, our findings may have far-reaching public health implications. Additional studies are needed to determine whether this relation is causal."
Itkonen, 2013	Associations Among Total and Food Additive Phosphorus Intake and Carotid Intima-Media Thickness – a Cross-Sectional Study in a Middle-Aged Population in Southern Finland	General population	"Our results indicate that a significant linear trend exists between energy-adjusted [total phosphorus] intake and [food-additive phosphate] intake, and [intima-media thickness] among all subjects. Based on these results, high dietary [phosphorus] intake should be further investigated due to its potential association with adverse cardiovascular health effects in the general population . . . . Our results show significant linear trends in the associations among energy-adjusted dietary phosphorus intake, food additive phosphorus intake and carotid intima-media thickness in a healthy, middle-aged Caucasian population. Based on these results, high dietary [phosphorus] intake should be further investigated due to its potential association with [cardiovascular disease] risk factors in the general population, not only in renal patients. Furthermore, prospective, or even better, long-term intervention studies are required to evaluate the possible impact of dietary [phosphorus] burden on risk of [cardiovascular disease]."
Adatorwovor, 2015	Intakes of Calcium and Phosphorus and Calculated Calcium-to-Phosphorus Ratios of Older Adults: NHANES 2005 to 2006 Data	General population	"Prospective randomized controlled trials of experimental subjects fed diets containing different Ca:P ratios are needed to clarify the concerns about potential adverse skeletal effects and fractures resulting from the consumption of low Ca:P ratio diets. Additional research is needed to examine the relationship between Ca:P ratio and potential health effects on bone mineral density . . . . Dietary phosphorus (P) intakes, on the other hand, have been shown to greatly exceed current gender-specific RDAs. The intakes of P, however, may be even greater than reported because information on phosphorus food additives is not available to scientists or the public for use in generating total P amounts in the diet."
Chang, 2014	High Dietary Phosphorus Intake is Associated with All-Cause Mortality: Results from NHANES III	General population	"In conclusion, high phosphorus intake was associated with increased mortality in a nationally representative, healthy US population. Because of prevalence of high phosphorus intake in healthy adults and the widespread use of inorganic phosphorus additives in processed food, our findings may have far-reaching public health implications. Additional studies are needed to determine whether this relation is causal."
Itkonen, 2013	Associations Among Total and Food Additive Phosphorus Intake and Carotid Intima-Media Thickness – a Cross-Sectional Study in a Middle-Aged Population in Southern Finland	General population	"Our results indicate that a significant linear trend exists between energy-adjusted [total phosphorus] intake and [food-additive phosphate] intake, and [intima-media thickness] among all subjects. Based on these results, high dietary [phosphorus] intake should be further investigated due to its potential association with adverse cardiovascular health effects in the general population . . . . Our results show significant linear trends in the associations among energy-adjusted dietary phosphorus intake, food additive phosphorus intake and carotid intima-media thickness in a healthy, middle-aged Caucasian population. Based on these results, high dietary [phosphorus] intake should be further investigated due to its potential association with [cardiovascular disease] risk factors in the general population, not only in renal patients. Furthermore, prospective, or even better, long-term intervention studies are required to evaluate the possible impact of dietary [phosphorus] burden on risk of [cardiovascular disease]."

(*Continued*)

Table 13–Continued.

First author, Year	Title	Focus[a]	Illustrative Verbatim Quotations
Wulaningsih, 2013	Inorganic Phosphate and the Risk of Cancer in the Swedish AMORIS Study	General population	". . . to our knowledge there are no observational studies describing the association between Pi and cancer risk in humans . . . . Pi is also found as an additive in processed food such as hamburgers and pizza, and as phosphoric acid in soda beverages. Mostly, this Pi content is not listed as an ingredient per se, and it was reported that this 'hidden' Pi content of food with Pi-containing additives is nearly 70% higher than in food without additives . . . . Considering the emerging experimental evidence linking Pi and cancer, it is of interest to explore this relation in an observational population-based setting . . . "
Dhingra, 2010	Relations of Serum Phosphorus Levels to Echocardiographic Left Ventricular Mass and Incidence of Heart Failure in the Community	General population	"Participants in our study were mostly middle-aged and of European descent, which limits the generalizability of our results . . . . In our large community-based sample of individuals without prior MI or CKD, serum phosphorus within the 'normal range' was associated with greater LV mass cross-sectionally, and with increased risk of heart failure prospectively."
Dhingra, 2007	Relations of Serum Phosphorus and Calcium Levels to the Incidence of Cardiovascular Disease in the Community	General population	"Surveys conducted by the US Department of Agriculture demonstrate an increase in the dietary intake of phosphorus among Americans, accompanied by a gradual decline in intake of calcium over the past 2 decades. Although the significance of increased consumption of phosphorus is unclear, limited data suggest that greater dietary intake of phosphorus may be associated with higher serum phosphorus levels. The Institute of Medicine has formulated dietary reference guidelines for phosphorus intake for Americans that suggest higher phosphorus levels may not be associated with adverse health effects in the general population. These dietary references have been questioned because the rising dietary phosphorus intake is paralleled by a greater risk of fractures and lower bone density among children. In the present study, we did not assess dietary phosphorus intake. Further research is warranted, therefore, to evaluate if a higher dietary intake of phosphorus translates into a greater risk for CVD in the general population by contributing to higher serum phosphorus levels."
Tucker, 2006	Colas, but not Other Carbonated Beverages, are Associated with Low Bone Mineral Density in Older Women: the Framingham Osteoporosis Study	General population	"Intake of cola, but not of other carbonated soft drinks, is associated with low BMD in women. Additional research is needed to confirm these findings . . . . The role of phosphoric acid on bone loss requires additional investigation. No evidence exists that occasional use of carbonated beverages, including cola, is detrimental to bone. However, unless additional evidence rules out an effect, women who are concerned about osteoporosis may want to avoid the regular use of cola beverages."
Sharkey, 2003	Summary Measure of Dietary Musculoskeletal Nutrient (Calcium, Vitamin D, Magnesium, and Phosphorus) Intakes is Associated with Lower-Extremity Physical Performance In Homebound Elderly Men and Women	General population	". . . the results of the current study suggest the need to explore strategies that target the improvement of dietary intake and physical performance. Further investigation is required to delineate the interrelations of nutritional status and physical performance in contributing to the functional decline in homebound elderly persons."
Moore, 2015	Association of Dietary Phosphate and Serum Phosphorus Concentration by Levels of Kidney Function	CKD	"It seems prudent for the Nutrient Facts Label to include phosphorus but also for food manufacturers to consider alternatives to phosphate additives."
Lou-Arnal, 2013	The Impact of Processing Meat and Fish Products on Phosphorus Intake in Chronic Kidney Disease Patients	CKD	"The use of phosphate additives in meat and fish processing leads to a phosphorus overload that we cannot quantify through labeling or food composition tables . . . . On reviewing the subject, we find that there is an accumulation of bad news about the use of phosphorus additives . . . "
Murtaugh, 2012	Dietary Phosphorus Intake and Mortality in Moderate Chronic Kidney Disease: NHANES III	CKD	"High dietary phosphorus intake is not associated with increased mortality in moderate CKD, presumably because serum phosphorus levels are maintained in the normal range at this level of GFR. Interventional trials are needed to define optimal phosphorus intake in moderate CKD."
Hsu, 2002	Elevations of Serum Phosphorus and Potassium in Mild to Moderate Chronic Renal Insufficiency	CKD	"Increases in serum phosphorus and potassium levels are apparent even among people with mild to moderate [chronic renal insufficiency]. These findings should be broadly generalizable to the larger [chronic renal insufficiency] population in the United States. Subtle elevations in serum phosphorus might contribute to the initiation and maintenance of secondary hyperparathyroidism, which is known to occur in mild to moderate [chronic renal insufficiency]."

BMD, bone mineral density; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; LV, left ventricular; MI, myocardial infarction; P, phosphorus; Pi, inorganic phosphorus; RDA, recommended dietary allowance; US, United States.
[a]"General population" is also used to indicate subpopulations other than those defined by the presence of CKD.

"long-term intervention studies" (Itkonen and others 2013). Several of the authors refer to the public health implications of the studies they report and to the implications their research holds for the general population (for example, the reports by Chang and others 2014 and Itkonen and others 2013). Some reports explicitly call into question reference ranges in use for serum phosphorus concentrations (Dhingra and others 2007; Dhingra and others 2010). Two reports state that accurate information on the TP and phosphate additive content of food is not available (Lou-Arna and others 2013; Adatorwovor and others 2015). One report contains advice for individuals (Tucker and others 2006), and another contains recommendations for interventions in a subpopulation (Sharkey and others 2003); the latter publication reports a study that was conducted in a population many of whom had generally deficient diets and inadequate dietary phosphorus intake. Moore and others (2015) considered it "prudent" for food manufacturers to consider alternatives to food-additive phosphate.

In summary, most authors of the review and primary research publications cited above expressed concerns about the safety of the amounts of phosphorus and phosphate food additives in the diets of the populations they studied, and several advocated measures aimed at reducing these amounts, including mandatory labeling of foods with phosphorus content and restriction of the use of phosphate additives in food. At the same time, they generally expressed awareness of the limitations of the evidence available and encouraged the conduct of further research, especially interventional studies. The national and international sets of guidelines cited above either report insufficient evidence currently available to determine ULs for dietary phosphorus, or they determine ULs that exceed the intakes of most populations. A report by the World Health Organization noted "sufficient evidence" of the carcinogenicity of processed meat, but the report did not mention phosphates.

Summary

This white paper presents the outcome of an extensive literature review focused on identifying evidence that substantiates or refutes associations of total dietary phosphorus and food-additive phosphate intake with health in humans. Relevant primary research articles published from 1995 to December 2015 were reviewed. Only 2 primary research publications were identified that focused on data potentially specific to a direct association between a phosphorus food additive and a clinical outcome. The majority of publications presented only indirect evidence: their data related only to intermediate linkages in various chains of effects or noncausal associations that reach from dietary food-additive phosphate intake to health, morbidity, or mortality. These publications reported findings about associations, noncausal or causal, between dietary food-additive phosphate intake; total dietary intake of phosphorus; phosphorus absorption and excretion; serum phosphorus concentration; relevant hormonal and other physiological changes; relevant target organ function and biomarkers of such function; and health or morbidity and mortality. The paucity of direct evidence (as well as the limitations of indirect evidence) is corroborated by the statements of authors of several publications reviewed for the white paper.

In the United States, food additives are defined in 21 United States Code 321 and the definition excludes substances deemed GRAS by FDA. More than 20 different phosphate salts used as food additives, as well as phosphoric acid, are so recognized. Very few of the primary research publications that examined possible associations of phosphate food additives with health, morbidity, or mortality specified which phosphate compounds were investigated; nevertheless, all compounds concerned would be expected to appear on the FDA list of GRAS substances. To this extent, the FDA definition, as it stands, was not applied in the white paper. Rather, the subject matter of the white paper was determined by primary research publications selected from PubMed literature searches that included "food additive" and "additive(s)" as key terms in search strings.

A total of 110 primary research articles were included in the white paper review. Only 11 (10%) of these articles focused on various associations of dietary food-additive phosphates, of which 2 (2%) examined the associations between dietary food-additive phosphorus (specifically, phosphoric acid) and morbidity or mortality. Half of the articles (55 [50%]) focused on various associations of the TP content in the diet.

Analysis of the studies revealed an array of methodological limitations. Some of these limitations were common to many of the studies; every study was affected by at least one of the limitations. The limitations weakened the reliability of the findings of the studies, decreased the strength of the evidence they could provide for or against the safety of dietary food-additive phosphate, and accounted, in part, for the numerous inconsistencies among the studies in their findings.

Phosphorus content in food

There are many well-recognized difficulties and limitations in adequately quantifying dietary intake of food-additive phosphate and organic phosphate. Five studies examined these difficulties. Two studies report that the use of food composition tables overestimated the nutrient composition of meals; one study identified differences in phosphorus content of meals analyzed by different methods (Navarro-Alarcon and others 2012) and the other study that food composition tables overestimated the calcium, magnesium, and phosphorus intakes in nutritional trials (Moreno-Torres and others 2001). The difference may have been attributed to differences in geographic location and technological and cooking processes. Two studies report that dairy foods and products, meats, and cereal and cereal products were the principal sources of phosphorus intake in Western Europe and in Japan (Sugiyama and others 2009; Welch and others 2009) and another study reports seasonal variations in phosphorus intake that corresponded to the seasonal variations in food availability and preparation (Sugiyama and others 2009).

Dietary phosphorus and serum phosphorus concentration

The associations of total dietary phosphorus or food-additive phosphate with serum phosphorus levels were described in 4 publications. Only one primary research publication directly assessed the relationship between food-additive phosphate and serum phosphorus concentration as a primary endpoint (Moore and others 2015). The analyses showed no direct relationship between consumption of food-additive phosphate and serum phosphate levels. However, the authors concluded that adjusting for kidney disease revealed a dietary association with serum phosphorus concentration that was stronger for foods having phosphate additives than for those without phosphate additives. Three studies evaluated associations of serum phosphorus concentrations with total dietary phosphorus intake. The results from 2 of these studies did not demonstrate a significant correlation between the intake of total dietary phosphorus and plasma phosphorus levels (Mataix and others 2006; Yamamoto and others 2013). In one study, a circadian pattern of serum phosphorus concentration was observed in

patients with CKD that was modified by dietary phosphorus intake (Ix and others 2014).

Serum phosphorus concentration and target organs and biomarkers

The next linkage examined in the white paper involves associations of serum phosphorus with target organs or biomarkers. The results from 3 observational studies showed a statistically significant association between serum phosphorus concentrations and changes in target organs or biomarkers. In one of these studies, there was a significant negative correlation between BALP activity and serum phosphorus concentration (Haraikawa and others 2012). The results from another observational study revealed that higher serum phosphorus levels were associated with greater LVM in men but not in women, and with increased odds of LVH in men and decreased odds in women (Saab and others 2010). The 3rd observational study that evaluated subjects over 6 y determined that higher serum phosphorus concentrations were an independent predictor of new onset and worsening CAC, similar to other risk factors, including baseline CAC scores, lower eGFR levels, and traditional CVD risk factors (Tuttle and Short 2009).

Serum phosphorus concentration and hormonal and other physiological changes

Five published studies included 2 observational studies, 1 randomized, controlled trial, and 2 interventional studies that described associations of serum phosphorus concentrations with regulatory hormones and physiological outcomes, mostly assessed as changes in serum PTH levels. Three of these studies report no association of serum phosphorus with serum PTH concentrations in healthy subjects: the study populations and dietary phosphorus sources varied between studies (Brot and others 1999; Antoniucci and others 2006; Bansal and others 2013); however, 2 of the studies demonstrated statistically significant associations (Antoniucci and others 2006; Bansal and others 2013). A direct correlation of serum PTH concentrations with serum phosphorus levels in both older and younger men was described in another study (Portale and others 1996). Another study reported that high serum phosphorus levels after a phosphate supplement increased serum PTH concentrations, whereas high serum phosphate concentrations from meat and whole grains did not affect serum PTH levels and high serum levels from cheese products were associated with decreased serum PTH levels (Karp and others 2007).

Serum phosphorus concentration and clinical outcomes

The associations between serum phosphorus concentrations and morbidity or mortality were evaluated in 13 observational studies and in one case–control trial, and included examinations of associations with CVD, cancer, diabetes, and death (Table 3). Most studies noted an association between high serum phosphorus concentrations and adverse clinical outcomes. Results from 9 of these studies demonstrated that higher serum phosphorus levels were associated with increased risk of incident CVD. Higher serum phosphorus concentrations were associated with an increased risk of cardiovascular mortality in 5 of the studies; in 3 of the 5 studies, increased risk of death and cardiovascular events were observed in people who had prior CVD or MI. In some of these studies, serum levels that were within the reference ranges were also associated with adverse clinical outcomes. In one such study, higher serum phosphorus concentrations that were within the reference range were associated with higher pulse pressure and lower large and small artery elasticity in individuals without prior CVD (Ix and others 2009). The results from another such study note that after 15 y of follow-up of in healthy individuals, higher serum phosphorus levels, even within the normal range, were associated with higher coronary artery calcium scores (Foley and others 2009). One study found a greater overall cancer risk associated with higher serum phosphorus levels in healthy men while a negative association of incident cancer with higher serum phosphorus levels was reported in healthy women (Wulaningsih and others 2013). Associations with progression of diabetes and renal disease were described in 2 studies. High serum phosphorus concentrations were associated with progression to T2D in healthy individuals in one of these studies (Lorenzo and others 2014), and individuals with high serum phosphorus concentrations that were within the normal range were associated with a 2-fold higher risk of developing new onset CKD and ESRD in another study (O'Seaghdha and others 2011). Associations of serum phosphorus levels with death were reported in 4 studies, whereas one study showed no such association. One study found that, for serum phosphorus levels greater than 3.5 mg/dL, every 1 mg/dL increase was associated with a 35% increased risk of all-cause death (Chang and Grams 2014). However, low baseline serum phosphorus concentrations were associated with an increased risk of death within 12 wk of initiating ART in immunocompromised HIV-infected individuals (Heimburger and others 2010).

Dietary phosphorus and target organs and biomarkers

The associations of dietary phosphorus with changes in target organ effects or biomarkers were described in 16 primary research publications. Associations with food-additive phosphorus were evaluated in 3 of the 16 studies. Analysis of results from one observational study revealed that LDL-C/HDL-C ratio, serum triglycerides, eGFR, HbA1c%, TP, and energy intake were significantly and directly associated with changes in food-additive phosphate intake but that there were no statistically significant associations of food-additive phosphate intake with plasma FGF-23, serum iPTH, serum 25(OH)D concentrations, or in Ca:P ratios (Itkonen and others 2013). Two studies evaluated the association of consumption of colas that contained phosphoric acid with differences in BMD. One study did not find a clear association of differences in BMD in men with the amounts of food-additive phosphorus (consisting of colas) consumed, with Ca:P intake ratios, or with the quantity of phosphoric acid in carbonated drinks; however, an association between caffeinated cola beverage intake and hip BMD was seen in women (Tucker and others 2006). A short-term study that evaluated consumption of low Ca:P diets in which cola was substituted for milk demonstrated significant increases in biochemical markers of bone turnover in the cola arm compared with isoenergetic intake of 2.5 L milk when each was consumed with the same low-calcium diet (Kristensen and others 2005). Negative associations between phosphorus intake and IMT or lower BMD observed in 2 studies were primarily manifested in women; there was no explanation of the sex association of these results.

Twelve of the 16 studies evaluated the association of total dietary phosphorus and target organs or biomarkers; 4 studies evaluated associations of dietary phosphorus with biomarkers of CVD and 8 studies evaluated associations with biomarkers of bone metabolism. Eleven studies were in observational cohorts and one study was a double-blind, crossover trial. The studies that evaluated biomarkers of CVD found, variously, that dietary phosphorus was associated with either decreased or increased risks of manifestations of CVD. Increases in dietary phosphorus were associated with greater LVM and with LVH (Yamamoto and others 2013), reduced systolic

and diastolic BP (Alonso and others 2010), and with decreases in endothelial dilation measured by %FMD (Shuto and others 2009). One study did not find a relationship between dietary phosphates and CAC (Kwak and others 2014). In studies that evaluated biomarkers of bone metabolism, 4 studies reported direct associations between dietary phosphorus and BMD and/or BMC in adults and in children (Teegarden and others 1998; Bounds and others 2005) while one study did not find an association with BMD in postmenopausal women (Méndez and others 2002) and one study reported that dietary phosphates were negatively correlated with BMC in healthy female children. One study noted a positive association of dietary phosphate consumption during pregnancy with BMD in the children born of these pregnancies at age 8; however, a 2nd study in the same birth cohort did not find an association at age 16 (Jones and others 2000; Yin and others 2010). One study determined that dietary phosphorus was negatively correlated with BALP in Japanese adults (Haraikawa and others 2012).

Dietary phosphorus and hormonal and other physiological changes

The literature search identified 19 primary clinical research studies that evaluated the association of dietary phosphorus and physiologic outcomes. These studies examined changes in serum PTH hormone, FGF-23, vitamin D metabolite concentrations, and/or changes in calcium disposition in healthy adults and children. Three studies evaluated association of physiological outcomes with food-additive phosphorus, 8 studies evaluated associations of physiological outcomes with total dietary phosphorus, and 8 studies evaluated associations of physiological outcomes with load of ingested phosphorus.

The 3 studies that evaluated food-additive phosphorus analyzed different food sources of these additives and different physiological outcomes, and diverse results were reported. One study demonstrated that increased consumption of diets with food-additive phosphates (assessed as processed cheese consumption) compared with diets that contained organic phosphorus was associated with increases in serum PTH (Kemi and others 2009). Another study determined that consumption of cola beverages containing food-additive phosphorus (phosphoric acid) by healthy women was associated with production of urine with greater acid excretion compared with other beverages (Heaney and Rafferty 2001). Consumption of large amounts of Coca-Cola or Pepsi-Cola (containing phosphoric acid) by children was associated with reduced serum calcium levels (Mazariegos-Ramos and others 1995).

There were some similar findings in the 8 studies that evaluated associations of total dietary phosphorus and physiological outcomes, but the studies were very different in design, evaluated different physiological outcomes, and included different subpopulations. Most studies were observational cohorts. Two observational studies in healthy individuals demonstrated that greater intake of dietary phosphorus was directly associated with greater serum PTH and FGF-23 concentrations (Kemi and others 2010; Gutiérrez and others 2011). However, the results from 2 studies in healthy women showed no association between serum PTH and dietary phosphorus intake, calcium intake, or the calcium:phosphorus intake ratio (Brot and others 1999; Ito and others 2011). Other physiological outcomes were also evaluated. Dietary phosphorus intake was not associated with calcium absorption in one study (Heaney 2000), whereas another study demonstrated that milk enriched with TCP resulted in increased absorption of calcium (López-Huertas and others 2006).

Phosphorus load and hormonal and other physiological changes

Eight studies evaluated physiological effects associated with consumption of additional loads of phosphorus by using either phosphorus supplementation or consumption of additional food containing high amounts of phosphorus. Greater intake of dietary phosphorus was associated with increased serum PTH and FGF-23 concentrations in 2 observational studies and 2 interventional trials that evaluated diets in healthy individuals (Antoniucci and others 2006; Nishida and others 2006; Gutiérrez and others 2010; Kemi and others 2010). Another study reported serum PTH levels were unchanged after phosphate-/calcium-restricted meals while phosphate-/calcium-enriched meals led to a significant decrease of PTH levels (Vervloet and others 2011). The results of a short-term interventional study reported no changes in plasma PTH concentrations after the administration of 3 diets with different Ca:P ratios (implemented by varying amounts of calcium and maintaining daily phosphorus at 1000 mg in healthy individuals) (Trautvetter and others 2016). The food source of phosphorus and dietary supplementation with phosphates affected serum calcium and phosphate levels and urinary excretion of calcium and phosphorus (Karp and others 2007). Urinary phosphorus and calcium excretion were greater after consumption of meat products than after consumption of other foods containing phosphorus. However, serum PTH was decreased only after consumption of cheese and was not affected by other foods containing phosphates. In studies that evaluated associations with serum concentrations of $1,25(OH)_2D$, higher $1,25(OH)_2D$ levels were associated with phosphorus restriction and reduced concentrations were associated with phosphate supplementation (Antoniucci and others 2006). The association was different in elderly men; serum 1,25(OH)2D concentrations in these subjects were not significantly changed after phosphorus intake was increased but were increased after phosphorus restriction (Portale and others 1996).

A study that evaluated the short-term intravenous administration of phosphorus to increase serum phosphorus levels determined that iPTH increased and was 200% of baseline serum PTH levels at 4 h after the intravenous dose (Ito and others 2007). However, there were no changes in serum FGF-23 concentrations.

Dietary phosphorus and clinical outcomes

Selective concatenation of the findings from some of the studies discussed above may suggest associations of dietary phosphorus intake with morbidity or mortality and indicate possible directions for further research. In addition, persuasive pathophysiological models exist supporting the possibility of such associations. However, indirect inference cannot be substituted for data from studies designed to address the presence or absence of such associations directly. Furthermore, the findings of observational studies seeking to substantiate or refute associations between variables may well run counter to the outcomes of interventional trials addressing the same questions (FDA 2009). The literature search and selection performed for the white paper did not identify any interventional studies that directly investigated possible effects of dietary phosphorus on morbidity or mortality; the observational studies that directly examined possible associations between dietary phosphorus and clinical outcomes are discussed in this subsection.

Only 2 primary research publications possibly demonstrated a direct association between a phosphorus food-additive and a clinical outcome. These publications reported a positive association between consumption of cola beverages, which presumably contained phosphoric acid, and bone fracture in school-aged

children (Wyshak 2000; Ma and Jones 2004). An additional 20 publications reported associations between the total quantity of phosphorus in the diet and clinical outcomes without differentiating between food-additive and nonfood-additive phosphate. All these studies were observational studies: 15 were prospective cohort studies, 4 were case–control studies, and 3 were cross-sectional studies.

Of the 20 studies, half reported an association between dietary phosphorus and morbidity or mortality and half did not find an association. A higher intake of dietary phosphorus was associated with an increase in morbidity or mortality in 6 studies and with a decrease in 4 studies. Ten studies investigated possible associations between dietary phosphorus intake and cancer risk and a statistically significant association was noted in 3 studies: higher dietary phosphorus intake was associated with a higher risk for prostate cancer in 2 studies (Wilson and others 2015; Kesse and others 2006) (while no association was noted in 4 studies), and with a lower risk for colorectal tumor in one study (Kesse and others 2005). Three studies investigated associations between dietary phosphorus intake and bone health. One of these studies, in middle-aged and elderly men, found a lower fracture risk with higher intakes of total dietary phosphorus (Elmståhl and others 1998). The other 2 studies focused on cola beverages and are mentioned in the previous paragraph. Two studies evaluated associations between dietary phosphorus intake and all-cause mortality: one study reported that higher dietary phosphorus intake was associated with higher mortality in a population representative of the general U.S. population (Chang and others 2014), and one did not find an association between higher dietary phosphorus intake and death in a population with moderate CKD (Murtaugh and others 2012). Another study determined that higher dietary phosphorus was associated with lower progression in "multimorbidity" (Ruel and others 2014). Two studies investigated associations between dietary phosphorus intake and physical performance in older adults: higher intakes were associated with improved lower extremity performance in one of these studies, in which a quarter of subjects had dietary phosphorus intakes at or below the RDA (Sharkey and others 2003); in the other study, no association was reported between phosphorus intake and changes in muscle strength (Scott and others 2010).

Review articles, expert opinion, and commentary

Although no systematic literature search and selection was performed for publications other than primary research articles, other types of publications were encountered that discussed relationships between dietary phosphorus and human health. These articles included publications by authoritative bodies; academic review articles; primary research publications containing authors' discussions; and articles and information designed for and targeting the public at large (discussion of which is beyond the scope of the white paper). Most authors of the review articles and primary research publications expressed concerns about the safety of the amounts of phosphorus and phosphate food additives in the diets of the populations they studied, and several advocated measures aimed at reducing these amounts, including mandatory labeling of foods with phosphorus content and restriction of the use of phosphate additives in food. Nevertheless, these authors generally expressed awareness of the limitations of the evidence available and encouraged the conduct of further research, especially interventional studies. The national and international sets of guidelines examined either demonstrated insufficient evidence currently available to determine ULs for dietary phosphorus, or determined ULs that exceed the intakes of most populations; nevertheless, they note concerns about population-level increases in dietary phosphorus intake through soft drinks and foods containing phosphate additives (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board - Institute of Medicine 1997; European Food Safety Authority 2005, 2015; Otten and others 2006). A report by the World Health Organization reported "sufficient evidence" of the carcinogenicity of processed meat but the report did not mention phosphates (Bouvard 2015). EFSA will reevaluate the use of phosphates as food additives with high priority by December 31, 2018 (European Food Safety Authority 2015).

Overall Conclusions

According to prespecified criteria, 110 primary research publications were selected for inclusion in this white paper from those identified by an extensive PubMed literature search. The search targeted articles published from 1995 through 2015 that reported studies furnishing evidence directly or indirectly relevant to associations between the dietary intake of phosphorus and clinical outcomes. Only 2 published studies were identified that provided data potentially specific to a direct association between a phosphorus food additive (in both cases, phosphoric acid) and a clinical outcome.

Analysis of the studies revealed an array of methodological limitations. Some of these limitations were common to many of the studies; every study was affected by at least one of limitation. The limitations weakened the reliability of the findings of the studies, decreased the strength of the evidence they could provide for or against the safety of dietary food-additive phosphate, and accounted, in part, for the numerous inconsistencies among the studies in their findings. These methodological limitations included the following:

- Noninterventional study design, precluding assessment of possible causal roles of factors investigated
- Probable bias of findings by unrecognized confounding factors, notably in studies examining morbidity or mortality; incorporation of different selections of recognized confounders into the various statistical models employed within and across studies
- Inherent difficulties in determining dietary phosphorus intake and, in particular, the intake of food-additive phosphate: the inherent limitations of widely used dietary ascertainment methods, such as 24-h dietary recall and FFQs; likely inaccuracies in nutrient composition tables
- Inherent difficulties in determining the quantity of phosphorus absorbed from the diet
- The complex interrelationships between dietary phosphorus, conutrients (notably, calcium), and different foods, and the consequent difficulties of isolating the effects or noncausal associations of dietary phosphorus itself; difficulties in assessing the proportional contribution of food-additive phosphate to total dietary phosphorus intake and the effects of food-additive phosphate on total dietary intake
- The latencies, likely to be long, between dietary exposure and its effects on morbidity or mortality; the unproven validity of potential surrogate markers of morbidity and mortality, notably serum phosphorus concentration, that were assessed in studies of shorter duration; and widely varying durations of subject participation across the studies reviewed

- Differing boundaries used to define categories of dietary phosphorus intake across studies, and the variable relationships of these boundaries to dietary recommendations and *de facto* population intakes
- The diverse nature of the populations studied and their characteristic diets, the location of these populations in different countries, and changing dietary habits and methods of food production over the 20-y period during which the publications reviewed for the white paper were published

These and other limitations were discussed in many of the primary research publications reporting affected studies.

Of the studies included in the white paper that examined various associations of dietary food-additive phosphorus, very few specified which compounds were under investigation as additives. The (usually implicit) assumption in the studies was that changes in total dietary phosphorus intake or absorption resulting from the inclusion of food-additive phosphorus in the diet were central to the investigation and not the specific phosphorus additive(s) ingested.

Only one-third of the studies reviewed were interventional, allowing determination of causal relationships, and fewer than half of these studies allowed relationships of food-additive phosphate intake to be distinguished from those of total dietary phosphorus intake. No studies examining direct associations of food-additive phosphorus or total dietary phosphorus intake with morbidity or mortality were interventional.

The number of relevant studies in each area that was set off for separate analysis in the white paper was small. Where there were several studies in a given area, their results were often discordant or difficult to compare: this was striking among the studies examining direct associations of food-additive phosphorus or total dietary phosphorus intake with morbidity or mortality. In some areas, the findings of studies were in agreement: for example, exposures to higher quantities of dietary phosphorus were reported to be associated with potentially adverse physiological outcomes that included changes in serum PTH and FGF-23 concentrations in the 5 studies that investigated these relationships; and higher dietary phosphorus intake was associated with potentially beneficial changes in biomarkers of bone metabolism, primarily in children, in 4 studies. However, many of these studies were observational, few causal connections could be inferred, and, in the studies generating the data, differences in morbidity or mortality were not investigated.

Findings of studies that did not directly examine associations of food-additive phosphorus or total dietary phosphorus intake with morbidity or mortality could not (even in principle) be used to draw conclusions about relationships between these parameters. Studies that did examine these relationships directly were noted to have one or more of the important methodological limitations itemized above.

Firm conclusions about the safety and possible risks of food-additive phosphate in the general population could not be reached based on the clinical studies reviewed for the white paper. This outcome is consonant with the overall assessments of authoritative institutions that have concluded that the available data are insufficient to make the required determinations. These institutions include the United States' IOM and the EFSA; the latter will reevaluate the use of phosphates as food additives with high priority by December 31, 2018 (European Food Safety Authority 2015).

Despite the inadequacy of the evidence currently available, many of the authors of the publications reviewed for the white paper expressed concerns about the quantities of phosphorus and food-additive phosphate in the diets of the populations and subpopulations they studied, and these concerns have been noted by the authoritative bodies cited above. At the same time, most of these authors offered only qualified conclusions and expressed themselves tentatively. In addition, authors of primary research publications, authors of review articles, and authoritative institutions have called for the conduct of further research.

Abbreviations

%FMD	percent flow-mediated dilation
$1,25(OH)_2D$	1,25 dihydroxyvitamin D
$24,25(OH)_2D$	24,25-dihydroxycholecalciferol
25(OH)D	25-hydroxyvitamin D
ABI	ankle brachial index
aHR	adjusted hazard ratio
aLM	appendicular lean mass
ALP	alkaline phosphatase
AM	after modification
AMORIS	Apolipoprotein Mortality Risk Study
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AP	food-additive phosphate
ARIC	Atherosclerosis Risk in Communities Study
ART	antiretroviral therapy
ATBC	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study
AUC	area under the time-concentration curve
BALP	bone-specific alkaline phosphatase
BGP	osteocalcin
BM	before modification
BMC	bone mineral content
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcification
Ca	calcium
Ca:P	calcium to phosphate
CATO	Cato Research
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CPP	caseinophosphopeptides
CP-P	calcium–phosphorus product
CRP	C-reactive protein
CVD	cardiovascular disease
CTX	C-telopeptide
DBP	diastolic blood pressure
DEXA	dual-energy X-ray absorptiometry
DM	diabetes mellitus
DPD/Cr	urine deoxypyridinoline corrected for creatinine excretion
E3N-EPIC	Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study)
EFSA	European Food Safety Authority
eGFR	estimated glomerular filtration rate
EPIC	European Prospective Investigation into Cancer and Nutrition
ESRD	end-stage renal disease

ET	estrogen therapy
eTP	energy-adjusted total phosphorus
FDA	Food and Drug Administration
FEP	fractional excretion of phosphorus
FFQ	food frequency questionnaire
FGF-23	fibroblast growth factor 23
FHS	Framingham Heart Study
FOS	fructooligosaccharide
GFR	glomerular filtration rate
GRAS	generally recognized as safe
HbA1c%	glycosylated hemoglobin A1c (% of total hemoglobin)
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
iCa	ionized calcium
ICTP	serum crosslinked telopeptide of type I collagen
IFAC	International Food Additives Council
IMT	intima-media thickness
IOM	Institute of Medicine (now renamed "National Academy of Medicine")
iPTH	intact-parathyroid hormone
LDL	low-density lipoprotein
LDL-C/HDL-C	low-density lipoprotein cholesterol to high-density lipoprotein cholesterol
LV	left ventricular
LVH	left ventricular hypertrophy
LVM	left ventricular mass
MESA	Multi-Ethnic Study of Atherosclerosis
MI	myocardial infarction
MP	monophosphate
MRP	Maillard reaction products
MSS	milk solids
NA	not applicable
NAFS	Nutrition and Function Study
NHANES	National Health and Nutrition Examination Survey
NHANES III	Third National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
NP	natural phosphorus
NS	not specified
NTX	N-telopeptide
OR	odds ratio
P	phosphorus
Pi	inorganic phosphorus
PICP	serum carboxy-terminal propeptide of type I collagen
PMID	PubMed identification number
PP	polyphosphate
PTH	parathyroid hormone
r	correlation coefficient
RDA	recommended dietary allowance
RR	relative risk
RU	relative unit
SBP	systolic blood pressure
SE	standard error
SEHC	Scientific Evaluation of Health Claims
SU.VI.MAX	Supplementation en Vitamines et Mineraux Antioxydants
T2D	Type 2 diabetes
TCP	tricalcium phosphate
t.i.d.	3 times per day
TLGS	Tehran Lipid and Glucose Study
TP	total phosphorus
UL	tolerable upper intake level
ULN	upper limit of normal
U-NTx	24-h urinary N-terminal telopeptide of type I collagen
U-NTx/U-Cr	24-h urinary N-terminal telopeptide of type I collagen corrected for creatinine
US	United States
U.S.	United States
Vit D	vitamin D

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Appendix A

A1 Dietary phosphorus and population subgroups

The literature search conducted for the white paper includes a sponsor-specified focus on certain population subgroups defined by age and disease or by disease risk, including adolescents, elderly persons, kidney disease, cardiovascular disease (CVD), cancer risk, and all-cause mortality. In addition to the information presented by chain-linkages in Section "Phosphate Food Additives and Human Health" of the white paper, all articles selected for inclusion in the master clinical table (MCT) in Appendix D were reviewed to identify the most suitable age and disease subgroups (where applicable) for presentation in an age- and disease-specific appendix to the white paper. The number of articles related to a particular age group and disease or disease risk was considered when selecting the most appropriate categories. Articles related to the management of phosphorus intake and excretion in more severe degrees of renal impairment were excluded from the literature search and from the body of the white paper (by excluding publications that included the terms "binder," "dialysis," "hemodialysis," or "haemodialysis" in the title or abstract from the search results). However, these publications have been reviewed and are summarized separately in Appendix A1.2.1. Other articles reviewed in this section have been more fully summarized in Section "Phosphate Food Additives and Human Health" of the white paper.

A1.1 Subgroups defined by age. Fourteen articles (13 of them reporting observational studies) examined phosphorus in children and teenagers. In most of these studies, data relating to teenagers and younger children (some as young as 18 mo of age) were not distinguishable. These publications are therefore discussed together.

Studies of the associations of phosphorus intake as well as of dietary Ca:P ratio with BMD and various mineral and bone markers were reported in a large number of publications: data on men, women, and children of various ages were presented. Studies in women could be clearly separated into 2 age-defined categories, and are addressed in this section. These data, along with data from studies in children, men, or both men and women, are also presented in this appendix.

A1.1.1 Children and adolescents. There were a total of 14 relevant published clinical studies in children and teenagers: 11 articles reported associations of phosphorus intake (Mazariegos-Ramos and others 1995; Trachtman and others 1995; Szajkowski 1996; Wyshak 2000; Ma and Jones 2004; Bounds and others 2005; Sugiyama and others 2009; Yin and others 2010; Delgado-Andrade and others 2011; Ramezani Tehrani and others 2013; Lin and others 2014); and 2 reported associations of phosphorus levels in body fluids (serum and saliva) (Waller and others 2007; Hartman and others 2013). Narrative summaries of these studies follow; selected study designs and other additional study details are presented in Table A1.

Four studies reviewed the intake of specific foods in children and adolescents. Delgado-Andrade and others (2011) evaluated dietary phosphorus absorption and serum phosphorus concentrations after consuming foods with high and low MRPs. MRPs are formed during the nonenzymatic reaction of a reducing sugar with an amino acid, usually upon heating, and are responsible for the brown colors and flavors in many foods (for example, fried, grilled, breaded, and reheated foods). Dietary phosphorus absorption was reduced when foods high in MRPs were consumed, but there was no significant difference in serum phosphorus levels or urinary phosphorus excretion when a diet low in MRPs was consumed. The authors concluded that a diet high in Maillard reaction products had a negative influence on dietary phosphorus absorption, resulting in a nonsignificant trend to negative phosphorus balance. This report is summarized in Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes" of the white paper. Mazariegos-Ramos and others (1995) identified a statistically significant association between low serum calcium levels (≤2.2 mmol/L) and consumption of more than 1.5 L per week of soft drinks containing phosphoric acid (odds ratio [OR]: 5.27; 95% confidence interval [CI]: 3.17 to 8.75; $P < 0.001$). The investigators also reported a statistically significant increase in serum calcium levels and decrease in serum phosphorus levels 30 d after the

Table A1–Summary of studies assessing phosphorus in children and adolescents

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Trachtman and others (1995)	118 children with renal insufficiency (25 black, 93 white) 18 mo to 10 y (males and females)	Dietary phosphorus	Cross-sectional study Performed at 4 time points in a 6-mo period.	• Assessed association between dietary mineral intake, serum phosphorus levels, and BP in black compared with white children with renal insufficiency. • In black children, SBP and DBP were directly associated with Ca and P intake. In white children, DBP was directly associated with P intake. • In all children, PTH levels were directly associated with SBP and DBP (with stronger associations in white compared with black children).
Mazariegos-Ramos and others (1995)	57 cases; 171 age-matched controls 18 mo to 14 y (males and females)	Food additive intake (phosphoric acid containing cola drinks)	Case–control study	• Assessed association between hypocalcemia and intake of cola soft drinks. • A statistically significant association was identified between serum Ca $\leq$ 2.2 mmol/L and consumption of at least 1.5 L/week of cola drinks.
Sugiyama and others (2009)	90 3 to 5 y (males and females)	Total dietary intake	Prospective cohort study	• Assessed multiseasonal average daily intake of P in Japanese children. • 4.4% of participants were reported to be at risk for P deficiency.
Ramezani Tehrani and others (2013)	134 4 to 12 y (males and females)	Total dietary intake	Prospective cohort study	• Assessed association between dairy product, milk, Ca, and P intake and early menarche (defined as $\leq$12 y). • Higher intakes of P (>647 mg/d), as well as Ca and Mg, were associated with early onset of menarche in young girls.
Waller and others (2007)	64 children with renal failure 4 to 16 y (males and females)	Total dietary intake	Prospective cohort study	• Assessed BMD in children with renal failure. • A normal mean BMD *Z*-score for age and sex was attained when serum Ca, P, and PTH levels were maintained within normal range by dietary restriction and medication in children with renal failure.
Bounds and others (2005)	52 6 y and 8 y (males and females)	Total dietary intake	Prospective cohort study	• Assessed association between dietary and lifestyle factors, BMC and BMD. • Dietary P intake, as well as other nutritional factors, were positively associated with total BMD and BMC in children at age 8 y.
Lin and others (2014)	2248 6 to 12 y (males and females)	Total dietary intake	Cross-sectional study	• Assessed association with intake of Ca, P, and Mg and dental caries. • No association was found between dental caries and dietary P intake. • A higher prevalence of caries was associated with a lower dietary Ca:P ratio.

(*Continued*)

Table A1–Continued.

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Jones and others (2000)	173 8 y (males and females)	Total dietary intake (maternal)	Prospective cohort study	• Assessed association between maternal dietary intake during last 3 mo of pregnancy and BMD of the offspring at age of 8 y. • After adjusting for dietary variables and using linear regression models, the only statistically significant associations were between phosphorus and fat intakes and lumbar spine BMD. • The authors concluded that a child in the ideal exposure categories for K, Mg, P, protein, and fat had a 5% to 12% higher BMD at the age of 8 y.
Hartman and others (2013)	77 8 to 12 y (males and females)	Not applicable	Cross-sectional survey	• Assessed association between salivary phosphate level and risk of obesity. • Higher levels of P in the saliva, but not in the serum, were associated with obesity in children.
Szajkowski (1996)	24 9 to 14 y (males and females)	Total dietary intake	Prospective cohort study	• Assessed multiseasonal average daily intake of Ca, Mg, and P in school children resident in a region of Poland. • Polish primary school children consumed P in quantities higher than the recommended daily intake, and their Ca and Mg intakes were lower than recommended.
Ma and others (2004)	206 cases, 206 individually matched controls 9 to 16 y (males and females)	Potentially food additive intake (carbonated soft drinks, colas and milk drinks)	Case–control study	• Assessed association between soft drink and milk consumption, physical activity, bone mass, and upper limb fracture. • Cola but not milk and not carbonated beverage consumption was associated with increased wrist and forearm fracture in children.
Delgado-Andrade and others (2011)	20 11 to 14 y (males)	Total dietary intake	Randomized, crossover study	• Determination of P bioavailability in diets composed of low and high levels of MRP. • Dietary P absorption was reduced when foods high in MRP (such as fried, grilled, breaded, and reheated foods) were consumed compared with when a diet low in MRP was consumed.
Wyshak (2000)	460 Mean age ± SD: 15 y, 8 mo ± 10 mo (females)	Potentially food additive intake (colas)	Cross-sectional study	• Assessment of association between physical activity and cola and noncola carbonated beverage intake and fracture. • Bone fractures were associated with carbonated beverage intake, with the highest risk of bone fractures in active girls who consumed cola and noncola carbonated beverages.
Yin and others (2010)	216 16 y (males and females)	Total dietary intake (maternal)	Prospective cohort study	• Assessment of association between maternal dietary intake during last 3 mo of pregnancy and BMD and BMC of offspring at 16 y of age. • Higher P density in the maternal diet was associated with higher BMD in the 8-y-old offspring.

BMC, bone mineral concentration; BMD, bone mineral density; BP, blood pressure; Ca, calcium; DBP, diastolic blood pressure; K, potassium; Mg, magnesium; MRP, Maillard reaction products; P, phosphorus; SBP , systolic blood pressure.

withdrawal of all soft drinks containing phosphoric acid in 17 children (both hypocalcemic cases and controls). A summary of this article is provided in Section "Food-additive phosphate, regulatory hormones, and other physiological outcomes" of the white paper. Ma and Jones (2004) reported a population-based, case–control study examining associations of upper limb fracture risk with soft drink and milk consumption in children aged 9 through 16 y and exploring mediation of these associations by bone mineral density, physical inactivity, or milk intake. This report is summarized in Section "Food-additive phosphate and clinical outcomes" of the white paper. On the basis of their analyses, the authors consider it most likely that television and video watching and computer use (each among the covariates taken into account) increase both fracture risk (for wrist and forearm fractures) and cola intake. Nevertheless, they conclude that their findings suggest that "cola but not milk and not carbonated beverage consumption is associated with increased wrist and forearm fracture in children, suggesting that consumption of cola drinks should be limited in children," while at the same time pointing to apparent "mediators" of this association, including low bone mineral density and television, video, and computer watching, but not decreased milk intake. Wyshak (2000) showed a higher rate of fracture in girls who drank colas only (as opposed to both colas and other carbonated beverages) than in those who drank no carbonated beverages: OR = 2.7 (95% CI: 1.30 to 5.60); $P = 0.008$. This report is also summarized in Section "Food-additive phosphate and clinical outcomes" of the white paper.

Two studies assessed phosphorus metabolism in children with renal disease. Both studies detected associations between reduced dietary phosphorus intake and health benefits. In one study (Trachtman and others 1995), lower intake of phosphorus was associated with lower blood pressure (BP). In the other study (Waller and others 2007), maintenance of serum calcium, phosphorus, and parathyroid hormone (PTH) levels within normal ranges in children with renal failure was associated with attainment of normal BMD *Z*-score for height and sex. These studies are discussed further in Appendix A1.1.1.

Two further studies addressed phosphorus intake in pregnant women and the associated effects on bone mineral density in their offspring (Jones and others 2000; Yin and others 2010). The authors reported a positive association between maternal dietary intake of phosphorus and BMD in 8-y-old children, but no significant association was reported in 16-y-old children. These studies are discussed further in Appendix A1.2.5.

Ramezani Tehrani and others (2013) studied the associations between total dietary phosphorus intake and the early onset of menarche in prepubertal girls and determined that girls with phosphorus intake greater than 647 mg/d had an earlier menarche than girls with lower intakes. This article is summarized in Section "Growth and development and child dental health" of the white paper.

Bounds and others (2005) evaluated total dietary phosphorus intake, and its association with both bone mineral density and bone mineral concentration. The authors noted that phosphorus intake between the age of 2 and 8 y, as well as intakes of other nutrients and minerals, was positively correlated with total BMC and BMD at the age of 8 y. This article is more fully described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper.

Associations between total dietary phosphorus and the incidence of dental caries were evaluated by Lin and others (2014) who determined that the calcium-to-phosphorus intake ratio was inversely related to the prevalence of dental caries. A summary of this article is included in Section "Growth and development and child dental health" of the white paper.

Hartman and others (2013) investigated associations between levels of salivary phosphorus, serum phosphorus, and measures of obesity in a cross-sectional study. Levels of phosphorus in the saliva, but not in the serum, were associated with increased body mass index (BMI) and waist circumference. This article is summarized in Section "Serum phosphorus concentration and clinical outcomes" of the white paper.

In summary, studies were reviewed that evaluated dietary phosphorus in children. These diverse studies reported differences in phosphorus intake between groups of children in 2 countries, ranging from intakes above the dietary recommendations to possibly deficient intakes; differences in phosphorus absorption according to food preparation; direct associations of fracture risk with cola consumption; associations of reduced dietary phosphorus intake with health benefits in children with renal dysfunction; associations of higher dietary phosphorus intake by pregnant women with favorable measures of bone health in their offspring years later; adverse associations between lower dietary calcium to phosphorus ratios and the prevalence of dental caries; an association between higher dietary phosphorus intake and earlier onset of menarche; and an association of higher salivary phosphorus concentration with concurrent obesity. All the studies were observational with the exception of Delgado-Andrade and others (2011) and so the vast majority of findings were of noncausal associations only. Limitations of many of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake include those inherent in studies of observational design and the limited reliability of the methods used for quantification of dietary phosphorus intake. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.1.2 Young and premenopausal women. All 10 studies enrolling women in this age category evaluated associations of phosphorus intake with markers of calcium metabolism, markers of bone metabolism, or BMD. Of these studies, 2 measured BMD in young women (Teegarden and others 1998; Ito and others 2011), while the remainder assessed levels of relevant minerals, hormones, and markers in the serum and urine. Narrative summaries of these studies follow; selected study design and other additional study details are displayed in Table A3. Seven of the publications originated from the Calcium Research Department, University of Helsinki, and additional information about the studies reported in these publications is provided in Table A2.

A study in young, white American women found that protein, calcium, and phosphorus intake was independently associated with BMD of the spine and radius, and BMC of the spine (Teegarden and others 1998). This study is also described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper. Ca:P ratio was associated with total body BMD. Additional modeling suggested that there was a complex relationship between calcium, phosphorus, and Ca:P ratio for the spine and total body BMD. The authors postulate that increasing daily calcium intake from a mean of 1000 to 1400 mg/d would offset any calcium losses due to phosphorus and protein intake (mean: 76 g/d) in this population and would support the attainment of peak bone mass in these young women; this calcium intake was calculated assuming a phosphorus intake of 1000 mg/d, which is lower than the mean of 1356 mg/d noted in this study.

Table A2–Summary of articles produced by the Calcium Research Department, University of Helsinki (Kemi and others, Karp and others, and Kärkkäinen and Lamberg-Allardt)

Study reference and study design	Study arm or analysis group	Serum Pi	Serum iCa	Serum PTH	Urine Pi	Urine Ca	Serum $1,25(OH)_2D$	Markers of bone formation	Markers of bone resorption
Kärkkäinen and Lamberg-Allardt (1996) Study conducted in 2 separate 24-h phases. All meals and drinks standardized for 24-h study period and provided 375 mg Ca and 878 mg P. • Randomized, crossover study of 1500 mg P dissolved in water compared with water alone when administered at breakfast. • Randomized, crossover study of 500 mg P dissolved in water compared with water alone when administered t.i.d. (at breakfast, lunch and 1 h before dinner).	1500 mg P with breakfast (compared with water alone)	Increased (significant)	Decreased (significant, still within normal range) Remained significantly decreased at 6 h after dose	Increased (significant, peak at 30 min after dose) No significant correlation with change in serum Pi	Increased (significant, maximum of 349% at 4 h)	Decreased (significant)	Not studied	**PICP**: Decreased (significant) **BGP** No significant change **BALP** Decrease (significant)	**ICTP** Unaffected **DPD/U-Cr** Unaffected
	500 mg P t.i.d. (compared with water alone)	Increased (significant, peak at 10 h)	Decreased (trend, but not significant)	Increased (significant, maximal increase 3 h after last P dose)	Not mentioned	Decreased (significant)	Not studied	**PICP**: Decreased (not significant) **BGP** No significant change **BLP** Decrease (significant)	**ICTP** Unaffected **DPD/U-Cr** Unaffected
Kemi and others (2006) Randomized, crossover study of allocated P dose dissolved in berry juice and administered in 3 equal doses (at breakfast, lunch, and with a snack, 1 h before dinner). All meals and drinks standardized for 24 h study period and provided 250 mg Ca and 495 mg P. Randomized daily P doses were 0 (placebo), 250, 750, and 1500 mg.	All arms	Dose-dependent increase (significant) 11 subjects exceeded ULN (in 750- and 1500-mg arms)	Dose-dependent decrease (significant for 1500-mg dose) Still decreased at next day's fasting sample	Dose-dependent increase (significant) 4 subjects exceeded ULN (in 750- and 1500-mg arms)	Dose-dependent increase (significant for 750- and 1500-mg arms)	Dose-dependent decrease (significant for 750- and 1500-mg arms)	Positive correlation between postdose morning level and AUC-PTH	**BALP** Dose-dependent decrease (significant for 750- and 1500-mg)	**U-NTx/U-Cr** Dose-dependent increase (1500 mg)
Karp and others (2007) Randomized, crossover study of 1000 mg P (provided using various P rich food sources or a P salt) divided equally over 3 meals compared with a low P control arm. As far as possible, meals and drinks were standardized to provide 250 mg Ca and 500 mg P over 24 h (excluding the P source foods).	1000 mg P from meat	Elevated compared with control arm (significant)	No effect compared with control arm	No effect	Elevated compared with control arm (significant) (and more than grain or cheese arms)	Greater increase than P salt arm	Not studied	**BALP** No significant difference compared with other sessions for AUC Increased compared with control (and grain) arms in contrast analysis	**NTx** (not corrected for U-Cr due to marked difference between sessions) Increased compared with control session (significant)

(*Continued*)

Table A2–Continued.

Study reference and study design	Study arm or analysis group	Serum Pi	Serum iCa	Serum PTH	Urine Pi	Urine Ca	Serum $1,25(OH)_2D$	Markers of bone formation	Markers of bone resorption
Karp and others (2007) Randomized, crossover study of 1000 mg P (provided using various P rich food sources or a P salt) divided equally over 3 meals compared with a low P control arm. As far as possible, meals and drinks were standardized to provide 250 mg Ca and 500 mg P over 24 h (excluding the P source foods).	1000 mg P from meat	Elevated compared with control arm (significant)	No effect compared with control arm	No effect	Elevated compared with control arm (significant) (and more than grain or cheese arms)	Greater increase than P salt arm	Not studied	**BALP** No significant difference compared with other sessions for AUC Increased compared with control (and grain) arms in contrast analysis	**NTx** (not corrected for U-Cr due to marked difference between sessions) Increased compared with control session (significant)
	1000 mg P from cheese	Increased compared with other arms (significant) Remained higher at 24-h fasting sample than other arms (significant)	Increased compared with other arms (significant) Remained higher at 24-h fasting sample than grain and P salt arms (significant) and meat arm (not significant)	AUC decreased compared with other arms (significant) Remained lower at 24 h fasting arm than other arms (significant)	Increased compared with control arm (significant)	Increased compared with other arms (significant)	Not studied	No significant difference compared with other arms for AUC	Decreased compared with control arm (significant)
	1000 mg P from whole grains	Elevated compared with control (significant)	No effect compared with control arm	No effect	Elevated compared with control arm (significant)	No significant change	Not studied	No significant difference compared with other arms for AUC	Increased compared with control (not significant)
	1000 mg P as phosphate salts	Elevated compared with control (significant)	Lower than control arm (significant)	Increased compared with control arm (significant)	Elevated compared with control, grain or cheese arms (significant)	No significant change	Not studied	No significant difference compared with other arms for AUC	Increased compared with control (not significant)
Kemi and others (2008) Randomized, crossover study of allocated Ca dose, dissolved in sugar-free lemon juice, administered in 3 equal doses (at breakfast, lunch, and dinner). All meals and drinks standardized for 24 h and provided 1850 mg P and 480 mg Ca. Randomized daily Ca doses were 0 (placebo), 600, and 1200 mg	600 mg Ca (compared with 0-mg placebo arm)	No significant change (but >ULN in 6 of 12 subjects) (placebo arm >ULN in 8 of 12 subjects)	Increased and maintained (significant)	Decreased (significant) (>ULN in 6 of 12 subjects on control arm)	Decreased (not significant)	Increased (not significant)	Not evaluated	**BALP** No significant difference	**U-NTx/U-Cr** Decreased (significant)

(*Continued*)

Table A2–Continued.

Study reference and study design	Study arm or analysis group	Serum Pi	Serum iCa	Serum PTH	Urine Pi	Urine Ca	Serum $1,25(OH)_2D$	Markers of bone formation	Markers of bone resorption
	1200 mg Ca (compared with 0-mg placebo arm)	No significant change(but >ULN in 4 of 12 subjects)	Increased compared with placebo and 600-mg arms (significant). Level maintained compared with placebo arm	Decreased (significant) (mean percentage decrease was higher than 600 mg for all time points)	Decreased compared with placebo arm (higher than 600-mg arm) (significant)	Increased (significant)	Not evaluated	Decreased (not significant).	Decreased (significant)
Karp and others (2013) Randomized, crossover study of 1500 mg of allocated phosphate salt, administered as a drink in 3 equal doses (at breakfast, lunch, and dinner) compared with placebo. All meals and drinks standardized for 24 h and provided 500 mg P and 340 mg Ca.	1500 mg PP (compared with placebo arm)	Increased (significant) (No significant difference between MP and PP arms)	No significant difference between study arms	Increased (significant) (Increase was equal for both MP and PP salts.)	Increased (significant) (No significant difference between MP and PP arms)	Decreased (significant) (Decreased more than MP arm)	Not evaluated	Not evaluated	Not evaluated
	1500 mg MP (compared with placebo arm)	Increased (significant)	No significant difference between study arms	Increased (significant)	Increased (significant)	Decreased (not significant)	Not evaluated	Not evaluated	Not evaluated
Kemi and others (2009) Cross-sectional study analyzing P intakes from 4-d food record according to the following categories: total P intake, natural P intake (cheese and milk excluding processed cheese), additive P (processed cheese only).	Total P intake (highest compared with lowest quartile)	Not evaluated	Lower in highest compared with lowest quartile (significant)	Higher in highest compared with lowest quartile (significant)	Not evaluated	No evaluated	Not evaluated	Not evaluated	Not evaluated

(*Continued*)

Table A2–Continued.

Study reference and study design	Study arm or analysis group	Serum Pi	Serum iCa	Serum PTH	Urine Pi	Urine Ca	Serum $1,25(OH)_2D$	Markers of bone formation	Markers of bone resorption
	Milk and cheese consumption (divided into 2 groups: high compared with low consumers) A significant interaction was reported, with S-iCa, when ≥1.225 mmol/L.	Not evaluated	No significant difference	Higher in low consumers (not significant) (when S-iCa, ≥1.225 mmol/L, groups did not differ significantly, when iCa, <1.225 mmol/L, groups did differ significantly)	Not evaluated	No evaluated	Not evaluated	Not evaluated	Not evaluated
	Processed cheese intake (consumers compared with nonconsumers) Due to a significant interaction between processed cheese consumption and contraceptive users, contraceptive users were analyzed separately from nonusers	Not evaluated	No significant difference	Higher in consumers (not significant) Higher in consumers compared with nonconsumers if contraceptive users were excluded. (significant)	Not evaluated	No evaluated	Not evaluated	Not evaluated	Not evaluated
Kemi and others (2010) Cross-sectional study analyzing 4-d food record according to quartiles of molar Ca:P intake ratio	Quartiles compared to each other. Did not differ between quartiles	Did not differ between quartiles. No difference after adjustment for covariates	Differed significantly between the Ca:P quartiles (30% higher in 1st than others combined). Maintained after adjustments for covariates	(Corrected for U-Cr) 1st quartile tended to be higher when compared individually. Significantly higher when other quartiles combined. Maintained after adjustments for covariates	(Corrected for U-Cr) Significantly affected by Ca:P ratio (30% higher in 1st quartile than others combined). Maintained after adjustments for covariates	1st quartile tended to be higher (30% higher in 1st than others combined).	Not evaluated	Not evaluated	

$1,25(OH)_2D$, 1,25 dihydroxyvitamin D; AUC, area under the time-concentration curve; BALP, bone-specific alkaline phosphatase; BGP, serum osteocalcin; Ca, calcium; Ca:P, calcium to phosphorus intake ratio; DPD/Cr, urine deoxypyridinoline corrected for creatinine excretion; iCa, ionized calcium; ICTP, serum crosslinked telopeptide of type I collagen; MP, monophosphate; P, phosphorus; Pi, inorganic phosphorus; PICP, serum carboxy-terminal propeptide of type I collagen; PP, polyphosphate; PTH, parathyroid hormone; S-iCa, serum ionized calcium; t.i.d., 3 times per day; U-Cr, urine creatinine excretion; ULN, upper limit of normal; U-NTx/U-Cr, 24-h urinary N-terminal telopeptide of type I collagen corrected for creatinine.
"Significant" refers to statistical significance.

A similar study in young Japanese university students reported a lower daily calcium intake and Ca:P intake ratio than in the American study. In the Japanese study, both calcium intake and Ca:P intake ratio had statistically significant positive associations with BMD in the distal radius, but not in the lumbar spine or femoral neck. There was no significant negative association between phosphorus intake and BMD at any site (Ito and others 2011). This study is more fully described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper.

Seven of the articles presented in this section originated from The Calcium Research Department, University of Helsinki. Two studies evaluated the effects of habitual diets high in phosphorus on calcium and bone metabolism using cross-sectional analyses of data from the same study (Kemi and others 2009, 2010). These studies are described further in Sections "Food-additive phosphate, regulatory hormones, and other physiological outcomes" and "Total dietary phosphorus, regulatory hormones, and other physiological outcomes" of the white paper. Five studies investigated the acute effects of a high phosphorus intake on markers of calcium and bone metabolism using randomized, controlled trials in small groups of female subjects, and are presented in Sections "Serum phosphorus concentration, regulatory hormones, and other physiological outcomes", "Total dietary phosphorus, regulatory hormones, and other physiological outcomes", and "Load of ingested phosphorus" of the white paper (Kärkkäinen and Lamberg-Allardt 1996; Kemi and others 2006; Karp and others 2007; Kemi and others 2008; Karp and others 2013). These 7 studies are summarized in Table A2.

The 4 acute interventional studies presented in Table A2 demonstrated a statistically significant increase in serum phosphorus levels when diets low in calcium and high in either organic or food-additive phosphorus were administered (molar Ca:P ratio $\leq$0.5) (Kärkkäinen and Lamberg-Allardt 1996; Kemi and others 2006; Karp and others 2007; Karp and others 2013). Statistically significant increases in serum phosphorus were not detected in the single acute study where calcium intake was 600 mg/d or higher (Kemi and others 2008) or in the cross-sectional studies where calcium intake was considered adequate (Kemi and others 2009; Kemi and others 2010). There were statistically significant increases in serum PTH levels in the randomized, controlled study arms where phosphate salts were administered as supplements and daily calcium intake was 375 mg or lower (well below 1000 mg/d, referenced in one of the reports as the adequate intake level for women in this age group) (Kärkkäinen and Lamberg-Allardt 1996; Kemi and others 2006; Karp and others 2007; Karp and others 2013). During the interventional studies, serum PTH levels were unchanged or decreased (when compared with controls) in the high-phosphorus whole-food study arms, and in the supplement study arms when calcium intake was 600 mg/d or higher (Karp and others 2007; Kemi and others 2008; Kemi and others 2009; Kemi and others 2010). Of note, the cross-sectional study examining processed cheese as a source of additive phosphate identified a nonsignificant increase in PTH, which became significant when oral contraceptive users were excluded from the analysis (due to a significant interaction between processed cheese consumption and oral contraception). The authors of this study observed that, when serum levels of ionized calcium were greater than 1.225 mmol/L, there was no association between changes in PTH and the intake of milk and nonprocessed cheese. An inverse association between changes in PTH and the intake of milk and nonprocessed cheese was noted when calcium levels fell below this threshold (Kemi and others 2009). When increasing phosphate supplement doses were used, serum phosphorus, ionized calcium, and PTH changes were dose-dependent (Kemi and others 2006).

Heaney and others conducted a randomized, controlled study to examine the acute calciuric effects of various drinks in female habitual soft drink consumers (Heaney and Rafferty 2001). Urinary calcium excretion was significantly greater after consuming the 2 caffeine-containing beverages (and the milk drinks used as positive controls). The authors did not detect any excess calciuria in noncaffeinated, phosphoric acid-containing beverages and phosphoric acid did not increase the calciuric effects of the caffeinated beverages. Grimm and others (2001) investigated the impact of a 6-wk high-phosphate diet, when consumed in conjunction with adequate amounts of calcium, on markers of calcium and bone metabolism as well as renal function. There were no statistically significant differences in markers of calcium and bone metabolism between the control periods and the supplementation period.

In summary, direct associations were identified between BMD and calcium intake, and BMD and phosphorus intake, in American women (Teegarden and others 1998); and between BMD and calcium intake, and BMD and calcium-to-phosphorus intake ratio, in Japanese women (who were noted to consume less calcium than their American counterparts) (Ito and others 2011). A cross-sectional study reported that subjects in the lowest quartile of calcium-to-phosphorus intake ratio had increased serum PTH and increased urinary excretion of calcium and phosphorus than the other quartiles (Kemi and others 2010). (Calcium-to-phosphorus intake ratio and bone health is discussed further in Appendix A1.2.3) Caffeine, but not phosphoric acid, was associated with excess calciuria in habitual cola drinkers (Heaney and Rafferty 2001). (Cola consumption and bone health is discussed further in Appendix A1.2.3) Increased levels of serum phosphorus and PTH were noted in acute studies where high-dose phosphorus supplements were administered in association with a low calcium diet (and changes in these parameters were dose-dependent), whereas PTH was not increased when whole-food phosphorus sources were administered, or when calcium intake was considered adequate ($\geq$600 mg/d) (Kärkkäinen and Lamberg-Allardt 1996; Kemi and others 2006; Karp and others 2007; Kemi and others 2008; Karp and others 2013). Statistically significantly higher serum PTH concentrations were observed in consumers of processed cheese (a source of food additive phosphate) than in nonconsumers, and a significantly higher serum PTH concentration was detected in consumers of less milk and cheese when serum calcium levels were lower than the threshold of 1.225 mmol/L. Serum calcium levels were lowest and PTH levels highest in the highest quartile of phosphorus intake versus the lowest (Kemi and others 2009).

Findings from studies that manipulate phosphorus intake through the administration of phosphorus supplements, or the enforcement of other short-term dietary alterations, have limited application in predicting the effects of habitual diets that differ in phosphorus content. This and other relevant limitations of these studies are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

Data from these studies suggest complex interactions between dietary phosphorus intake, dietary calcium intake, dietary calcium-to-phosphorus ratio, regulatory hormones, and bone indices. A favorable association between higher dietary phosphorus intake and BMD was reported in one study. Adverse

associations were not reported between higher total dietary phosphorus intakes and BMD and also were not reported between higher phosphoric acid intake in colas and measures of calcium handling.

A1.1.3 Perimenopausal and postmenopausal women. Seven studies evaluated dietary phosphorus in perimenopausal and postmenopausal women. All 7 articles evaluated the relationship between dietary phosphorus and parameters associated with bone and calcium metabolism or BMD. Narrative summaries of these studies follow; selected study design and other additional study details are displayed in Table A3.

Tucker and others (2006) concluded that there was an association between cola intake and BMD of the hip in women enrolled in the Framingham Osteoporosis study. The study is described in Section "Food-additive phosphate, target organs, and biomarkers" of the white paper. Similar associations were seen with diet colas, and to a lesser degree with decaffeinated colas. Although the population included women aged as young as 29 y, 80% of the women evaluated were postmenopausal. A similar association was not seen in men.

Heaney and others published 2 papers derived from data collected during longitudinal metabolic balance studies in 191 women (Heaney 2000; Heaney and Nordin 2002). These studies are described in Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes" and Section "Food-additive phosphate, regulatory hormones, and other physiological outcomes" of the white paper. The authors assessed the association of phosphorus and protein with calcium absorption, and the impact of calcium on phosphorus absorption. Overall, they did not find an association between phosphorus and protein intake and calcium absorption efficiency, but higher calcium intake was associated with reduced phosphorus absorption. The authors conclude that these findings may have implications for older patients taking high-dose calcium supplements in the absence of adequate phosphorus intake.

Mendez and others (2002) did not find an association between dietary phosphorus or calcium intake and BMD of the heel or forearm in postmenopausal Mexican women. The study is described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper. A large percentage of both dietary calcium and phosphorus intake was derived from vegetable sources and only 15% of women met the 1500 mg/d calcium intake recommendation.

Brot and others evaluated the relationships between BMD, metabolites of vitamin D, and the calcium:phosphorus intake ratio in healthy perimenopausal women and determined that calcium intake and calcium-to-phosphorus intake ratio were positively associated with BMD and negatively associated with $1,25(OH)_2D$) (Brot and others 1999). The study is described in Section "Total dietary phosphorus, regulatory hormones, and other physiological outcomes" of the white paper. Levels of 25-OHD were also weakly associated with BMD.

Bansal and others (2013) explored the association between estrogen replacement therapy and markers of calcium and bone metabolism, as well as BMD in a subset of subjects. Mean serum phosphorus concentration was lower and fractional excretion of phosphorus (FEP) was higher in women on estrogen therapy. The adjusted results demonstrated that mean FGF-23 did not differ between women who used or did not use estrogen therapy. When considering the association between markers of mineral metabolism and BMD in the multivariate model, a statistically significant direct association was only apparent for levels of FGF-23. This study also provided evidence that estrogen replacement therapy had a significant association with markers of calcium and phosphorus metabolism, including lower mean serum calcium and phosphorus levels. The use of estrogen replacement therapy was significantly associated with higher BMD in multivariate models, and this association remained significant when all mineral metabolism measures were included in the model simultaneously.

In summary, 2 studies evaluated the associations between dietary intake of calcium, phosphorus, and BMD: one noted a positive association between calcium-to-phosphorus intake ratio and BMD (Karp and others 2007), while in the other (where most calcium and phosphorus was derived from vegetable sources) an association was not detected (Méndez and others 2002). The consumption of cola beverages was associated with low BMD of the hip (Appendix A1.2.3 includes further discussion about cola intake and bone health) (Tucker and others 2006). Heaney and others reported that higher dietary calcium intake was associated with decreased phosphorus absorption, but the converse association was not demonstrated; the authors state that these findings have implications for ensuring adequate phosphorus intake when prescribing high-dose calcium supplements in older patients (Heaney 2000; Heaney and Nordin 2002). The findings of Bansal and others (2013) show that HRT in postmenopausal women is associated with lower serum phosphorus concentrations and higher FEP in the urine. Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake include those inherent in studies of observational design and the limited reliability of the methods used for quantification of dietary phosphorus intake. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.1.4 The elderly. Phosphorus intake in the elderly was evaluated in 5 studies: of these, 2 considered the association between nutrient intake and musculoskeletal factors (Sharkey and others 2003; Scott and others 2010), one evaluated whether there were any age-related changes in phosphorus and vitamin D homeostasis in men (Portale and others 1996), one assessed intakes of phosphorus and calcium in the elderly (Adatorwovor and others 2015), and one investigated whether food composition tables accurately calculate intake of calcium, magnesium, and phosphorus (Moreno-Torres and others 2001). Narrative summaries of these studies follow; characteristics of the studies and study populations are tabulated in Table A5.

A cross-sectional study of homebound American adults receiving home-delivered meals noted that those with the lowest nutrient intakes (assessed according to a score that incorporated phosphorus and other nutrients) and highest BMIs had significantly worse levels of lower-extremity physical performance (Sharkey and others 2003). The study is notable for the fact that 26% of subjects had diets containing less than 105% of the RDA for phosphorus. The study is more fully described in Section "Physical performance" of the white paper.

The association between nutrient intake and aLM, rate of muscle loss, and muscle strength was evaluated in a longitudinal study by Scott and others (2010). Baseline intake of phosphorus, along with protein and other minerals, were positively associated with aLM at baseline and a positive change in aLM over 2.6 y. No nutrient was positively associated with muscle strength. This study is more fully described in Section "Physical performance" of the white paper.

Table A3–Studies examining associations between phosphorus intake and bone mineral density or markers of calcium and bone metabolism in relation to phosphorus intake in young and premenopausal women

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Teegarden and others (1998)	215 women Age 18 to 31 y	Total dietary intake	Cross-sectional study	• Associations between bone mineral measurements and dietary calcium, protein, and phosphorus in young American women were studied. • Positive correlation between protein, Ca, and P intakes and BMD of the radius and spine as well as BMC of the spine.
Ito and others (2011)	441 women Age 18 to 20 y	Total dietary intake	Cross-sectional study	• Associations between habitual dietary phosphorus and calcium intake, and bone mineral density in young Japanese women were studied. • Calcium intake and Ca:P ratio had significant positive associations with BMD in the distal radius, but not in the lumbar spine or femoral neck.
Kärkkäinen and Lamberg-Allardt, (1996)	10 women in Part 1 10 women in Part 2 Age 21 to 34 y	Supplement • Part 1: single dose of 1500 mg phosphorus in water, or placebo • Part 2: 3 doses of phosphorus (500 mg each) in water, or placebo	Randomized, controlled study	• Markers of Ca and bone metabolism were monitored for 24 h after a phosphate supplement was administered in conjunction with a low Ca diet. • Serum P and PTH concentration was increased, and serum Ca was decreased when compared with placebo. Markers of bone formation decreased.
Heaney and Rafferty (2001)	30 women Age 20 to 40 y	Food additive (phosphoric acid-containing drinks)	Randomized, controlled study (incomplete random block)	• Effects of various drinks on urinary Ca levels in habitual soft drink consumers were assessed. Study arms included milk as well as soft drinks with and without caffeine, with and without phosphoric acid, and with and without added sugar. • Increases in urinary calcium excretion were greater after consuming the 2 caffeine-containing beverages (with the exception of the positives control, milk). • The authors did not detect any excess calciuria in noncaffeinated, phosphoric acid-containing beverages and phosphoric acid did not increase the calciuric effects of the caffeinated beverages.
Grimm and others (2001)	10 women Age 23 to 29 y	Supplement	Controlled interventional study	• Markers of Ca and bone metabolism and parameters of renal function monitored during a 6-wk high P period as well as 2 control periods (before and after). • There were no statistically significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption, and renal function during the phosphorus-supplemented period.
Kemi and others (2006)	15 women Age 20 to 28 y	Supplement	Randomized, crossover trial	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate supplement (0, 250, 500, or 750 mg) was administered in conjunction with a controlled, low Ca diet. • Statistically significant increase in serum levels of P and PTH, and urinary P excretion in relation to increasing P doses. Load of phosphorus intake was inversely associated with serum concentrations of biomarkers of bone metabolism.
Karp and others (2007)	16 women Age 20 to 30 y	Total dietary intake (including 1 supplement arm)	Randomized, crossover trial	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate rich diet was consumed. Used different whole food P sources for each arm, with one phosphate supplement arm composed of common phosphate additives. • The effects of high P intake appeared to depend on the source of P consumed. Compared to the control, serum P increased by all sources, PTH only increased by P supplement (decreased by cheese, unchanged by meat and whole grains). Based on serum P and urinary P excretion, P from meat and supplements appeared to be absorbed better than P from whole grains.

(*Continued*)

Table A3–Continued.

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Grimm and others (2001)	10 women Age 23 to 29 y	Supplement	Controlled interventional study	• Markers of Ca and bone-metabolism and parameters of renal function monitored during a 6-wk high P period as well as 2 control periods (before and after) • There were no statistically significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption, and renal function during the phosphorus-supplemented period.
Kemi and others (2006)	15 women Age 20 to 28 y	Supplement	Randomized, crossover trial	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate supplement (0, 250, 500, or 750 mg) was administered in conjunction with a controlled, low Ca diet. • Statistically significant increase in serum levels of P and PTH, and urinary P excretion in relation to increasing P doses. Load of phosphorus intake was inversely associated with serum concentrations of biomarkers of bone metabolism.
Karp and others (2007)	16 women Age 20 to 30 y	Total dietary intake (including 1 supplement arm)	Randomized, crossover trial	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate rich diet was consumed. Used different whole food P sources for each arm, with one phosphate supplement arm composed of common phosphate additives. • The effects of high P intake appeared to depend on the source of P consumed. Compared to the control, serum P increased by all sources, PTH only increased by P supplement (decreased by cheese, unchanged by meat and whole grains) Based on serum P and urinary P excretion, P from meat and supplements appeared to be absorbed better than P from whole grains.
Kemi and others (2008)	12 women Age 21 to 40 y	Total dietary intake	Randomized, crossover trial	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized Ca supplement dose (0, 600, or 1200 mg) was administered in conjunction with a controlled, high-phosphate diet. • Increasing doses of Ca, S-PTH concentration decreased, serum ionized Ca concentration increased, and BALP did not change. The authors noted that the dietary Ca:P ratio was important and that high Ca intake may not be sufficient to overcome adverse effects of high dietary P intake on calcium metabolism.
Kemi and others (2009)	147 women Age 31 to 43 y	Total dietary intake and food additive P (latter equated with processed cheese intake)	Cross-sectional study	• Associations between markers of Ca metabolism and habitual diet, subcategorized by amount of natural and additive phosphate consumed. • Higher total habitual dietary P intake was associated with higher S-PTH levels and lower serum ionized Ca concentrations, even after equalized total dietary Ca intake. • Mean S-PTH was higher and mean serum ionized Ca lower among participants whose habitual total P intake was the highest compared with those whose intake was the lowest.
Kemi and others (2010)	147 women Age 31 to 43 y	Total dietary intake	Cross-sectional study	• Assessment of markers of Ca metabolism and their associations with habitual diet, categorized by quartiles of Ca:P intake ratio. • Results suggest that habitual diets with low Ca:P molar ratios may interfere with homoeostasis of calcium metabolism and increase bone resorption, as indicated by higher S-PTH and urinary calcium concentrations.
Karp and others (2013)	14 women Age 19 to 31 y	Food additive (controlled diet plus supplement)	Randomized, crossover trial	• Markers of Ca metabolism and renal function were monitored for 24 h after P supplement or placebo, plus low Ca diet, was consumed. • During both P salt sessions, there was an increase in serum phosphate, urinary phosphate, and S-PTH compared with placebo. Results suggest that polyphosphate salts binds to Ca more effectively than monophosphate salts in the small intestine.

BALP, bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; Ca, calcium; Ca:P, calcium-to-phosphate ratio; PTH, parathyroid hormone; S-PTH, serum intact parathyroid hormone.

Table A4–Markers of calcium and bone metabolism in relation to phosphorus intake in perimenopausal and postmenopausal women

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Tucker KL and others, 2006	1413 women Age 29 to 83 y (80% post-menopausal) (2538 total subjects)	Food additive as cola beverages (total dietary intake also assessed)	Cross-sectional study	• Relationship between cola intake (and other carbonated beverages) and BMD. • Intake of cola (but not of other carbonated soft drinks) is associated with low BMD in women (cola consumers had significantly lower intakes of Ca and lower Ca:P intake ratios than individuals who did not consume colas).
Heaney RP, 2000	191 women Age 35 to 77 y	Total dietary intake	Longitudinal cohort study	• Assessment of whether P or protein intake is associated with differences in Ca absorption (567 unique metabolic balance studies included). • There was no relationship between the relative absorption of Ca and either P or protein intake.
Heaney RP and others, 2002	191 women Age 35 to 65 y 88 women Age 19 to 78 y (636 total subjects)	Total dietary intake (including all supplements)	Longitudinal cohort study (plus cross-sectional study)	• Association between Ca intake and absorption of dietary P (by measuring dietary intake and fecal elimination of Ca and P). • Ca intake increased without a corresponding increase in P intake, P absorption fell.
Méndez RO and others, 2002	47 women Age 45 to 63 y	Total dietary intake	Cross-sectional analysis	• Associations between dietary P, and Ca intake and excretion, anthropomorphic measures, estradiol level, and BMD in postmenopausal Mexican women. • No association was detected between dietary P or Ca intake and BMD of the heel or forearm.
Bansal N and others, 2013	2767 women Age 45 to 84 y	Not evaluated	Cross-sectional study (from Multi-Ethnic Study of Atherosclerosis)	• Assessment of the association between estrogen therapy and serum Ca and P, FGF-23, urinary excretion of Ca and P, 24,25 dihydroxyvitamin D, and PTH. • Assessment of the association between estrogen therapy and BMD. • Estrogen replacement therapy had a significant association with markers of Ca and P metabolism, including lower mean serum Ca and P levels.
Brot C and others, 1999	510 women Age 45 to 58 y	Total dietary intake	Cross-sectional study	• Associations between BMD, Vit D metabolites, and Ca:P intake ratio in healthy Danish perimenopausal women. • Ca intake and Ca:P intake ratio were positively associated with BMD and negatively associated with serum $1,25(OH)_2D$.

$1,25(OH)_2D$, 1,25 dihydroxyvitamin D; BMD, bone mineral density; Ca, calcium; FGF-23, fibroblast growth factor 23; P, phosphorus; PTH, parathyroid hormone; Vit D, vitamin D.

Moreno-Torres and others (2001) determined that food composition tables significantly overestimated intakes of calcium, magnesium, and phosphorus in elderly institutionalized adults in Granada, Spain, when compared with the duplicate diet technique. This study also is more fully described in Section "Phosphorus content in foods" of the white paper.

Portale and others (1996) reported that in both young and elderly healthy men, dietary phosphorus can be a major determinant of serum $1,25(OH)_2D$. In addition, both fasting and 24-h mean serum phosphorus levels in elderly men were lower than those of young men fed the identical diet, while levels of $1,25(OH)_2D$ were comparable. Mean serum phosphorus concentrations at 24-h decreased significantly when phosphorus intake was reduced from 2300 to 625 mg/d and the magnitude of the decrease was slightly greater in elderly men but this difference was statistically insignificant. This study is described in Section "Association of phosphorus load with regulatory hormones and other physiological outcomes" of the white paper.

Using data from the NHANES 2005 to 2006 survey, Adatorwovor and others (2015) evaluated calcium and phosphorus intakes, as well as the calcium-to-phosphorus intake ratio in older adults. Women had a higher calcium-to-phosphorus intake ratio, owing to higher consumption of calcium supplements and calcium-containing foods, and reduced consumption of phosphorus containing foods, compared with men. The RDA of phosphorus was exceeded in the vast majority of participants and the calcium-to-phosphorus intake ratio of 07:1.0 (based on mass) was well below the RDAs for calcium and phosphorus (1.5:1.0). The authors state that the phosphorus dietary intake data did not include the amounts of phosphate additives used in food processing, and that intakes of phosphorus may have been greater than reported because information on phosphate food additives "was not available to scientists or the public." This study is described in Section "Phosphorus content in foods" of the white paper.

In summary, data from these studies showed beneficial associations of adequate intake of phosphorus (together with other nutrients) in some subgroups of the elderly, some of whom were at risk of inadequate dietary intakes. However, the RDA for phosphorus was exceeded in the vast majority of almost 2000 subjects aged 50 y and older. Inconsistencies in determinations of phosphorus intake by different methods were identified in one study of the elderly, and fasting serum phosphorus concentrations were reported to be lower in elderly than in younger men in another. Limitations in the usefulness of evidence provided by these studies related to their design are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.2 Subgroups defined by disease or risk. The most commonly addressed diseases and risk factors covered in the reviewed articles occurred in subpopulations of persons with, or at increased risk of, the following: CKD, CVD, bone disease (low BMD, osteopenia, osteoporosis, and fracture risk), or cancer. Two articles addressed the diet of mothers and its association with BMD in their children.

A1.2.1 Chronic kidney disease. Chronic kidney disease is generally characterized by a gradual loss of kidney function over time. Kidney function is measured by calculating the glomerular

Table A5–Studies assessing phosphorus intake in the elderly

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Portale and others (1996)	7 elderly Mean age 71 ± 1 y 9 young Mean age 29 ±2 y (males)	Supplement	Prospective, crossover study	• Effect of aging on the metabolism of phosphorus and $1,25(OH)_2$ D in healthy men. • Direct correlation of serum PTH concentrations with serum P levels all men. Serum $1,25(OH)_2$D concentrations varied inversely with 24-h mean serum phosphorus concentrations and at any P concentration, $1,25(OH)_2$D was lower in elderly men than young men. • Fasting and 24-h mean serum P concentrations were lower in elderly men.
Moreno-Torres and others (2001)	112 subjects Mean age 83 ± 7 y (males and females)	Total dietary intake	Observational study	• Dietary intake of Ca, P, and Mg when assessed by food composition tables compared with duplicate diet technique. • The estimates based on food composition tables were higher than the values measured by direct chemical analyses: Ca, 6.7% to 9.5%; Mg, 26.9% to 33.1%; and P, 16.9% to 27.0%.
Sharkey and others (2003)	321 subjects Age ≥60 y (males and females)	Total dietary intake (excluding all dietary supplements)	Observational study	• Association between lower-extremity physical performance and summary nutrient intake of Ca, Vit D, Mg, and P. • A summary musculoskeletal nutrient score, calculated by adding quartiles of intake for Ca, Vit D, Mg, and P, was inversely associated with measures of lower extremity physical performance.
Scott and others (2010)	740 subjects Age 50 to 79 y (males and females)	Total dietary intake	Prospective cohort study	• Association between dietary intake of nutrients and aLM, muscle loss, and muscle strength of the knee extensors • Baseline intake of phosphorus, along with protein and other minerals, were positively associated with aLM at baseline and a positive change in aLM over 2.6 y. No nutrient was positively associated with muscle strength.
Adatorwovor and others (2015)	1992 subjects Age ≥50 y (males and females)	Total dietary intake (including all dietary supplements)	Observational study	• Intakes of Ca, P, and calculated Ca:P ratio in older adults in the NHANES 2005 to 2006 survey. • The RDA of P was exceeded in the vast majority of participants and the Ca:P intake ratio was well below the RDAs for Ca:P. Women had a higher Ca:P intake ratio than men, due to higher consumption of Ca supplements and Ca-containing foods, and reduced consumption of P containing foods.

$1,25(OH)_2$ D, 1,25-dihydroxyvitamin D; aLM, appendicular lean mass; Ca, calcium; P, phosphorus; Mg, magnesium; NHANES, National Health and Nutrition Examination Survey; RDA, recommended daily allowance; Vit D, vitamin D.

Table A6–Stages of chronic kidney disease

Stage	GFR (mL/min/ 1.73 m^2)	Description
1	≥90	Kidney damage with normal kidney function
2	60 to 89	Kidney damage with mild loss of kidney function
3a	45 to 59	Mild to moderate loss of kidney function
3b	30 to 44	Moderate to severe loss of kidney function
4	15 to 29	Severe loss of kidney function
5	<15	Kidney failure

Source: National Kidney Foundation.
GFR, glomerular filtration rate.

filtration rate (GFR) to determine the stage of chronic kidney disease CKD (Table A6). A GFR of <60 mL/min/1.73 m^2 or an albumin-to-creatinine ratio of ≥30 mg/g must be present for ≥3 mo for kidney dysfunction to be considered CKD. Phosphorus balance may be compromised by renal dysfunction, which may be accompanied by secondary hyperparathyroidism and increased serum FGF-23 concentration, each of which tends to increase urinary phosphorus excretion and maintain phosphorus balance through this and other mechanisms (National Kidney Foundation). A low-phosphorus diet or the administration of phosphate binders to patients in Stages 3 and 4 CKD are often recommended in an attempt to prevent hyperparathyroidism; however, clinical studies have yet to definitively demonstrate that lowering serum phosphorus can prevent hyperparathyroidism or elevated serum FGF-23 concentrations (Moe and others 2011).

A very large subset of the primary research articles originally identified for possible inclusion in the white paper reported studies of dietary phosphorus in relation to CKD. Subsequent incorporation of a clause in the search strings designed to exclude articles with the terms "binder," "hemodialysis," and "dialysis" revealed that between one-fifth and one-half of the articles originally identified included one of these terms in the title or abstract (Table B1). This emphasis in reported research is understandable: it is only in the subpopulation of persons with CKD that adverse effects of higher dietary phosphorus intake have been demonstrated, and demonstration of these effects has been limited to persons with late-stage renal disease, especially Stage 5, or end-stage renal disease (ESRD) (European Food Safety Authority 2015).

Nevertheless, several authors have expressed concern about possible adverse effects of high dietary phosphorus intake in persons with lesser degrees of renal compromise (for example, Ritz and others 2012 and Gutierrez 2013). Because such persons constitute a significant proportion of the population, any adverse effects could have public health implications: this is discussed further in the following 2 paragraphs.

NHANES data for the years 2007 to 2012 show that persons in the United States with Stages 1 through 3 CKD constituted approximately 13% of the population and fewer than 10% of these were aware of their condition. Persons with Stage 3 CKD alone constituted 5.9% of the population (95% CI: 5.33 to 6.47), and

only 8.5% of them were aware of their condition (National Health and Nutrition Examination Survey (a)).

The development of CKD has been regarded as a consequence of healthy ageing (Meyers 2015). NHANES data show that the prevalence of Stages 1, 2, and 3a CKD in U.S. persons 60 y and older is 23%. A 2008 review of CKD in population-based studies of persons aged 64 y and older reported that the prevalence of those with GFR less than 60 mL/min/1.73 m^2 in 4 studies (2 conducted in Canada, and 1 each in Finland and the United States) ranged from 23.4% to 35.8% (Zhang and Rothenbacher 2008). Furthermore, the world population is ageing (United Nations Dept. of Economic and Social Affairs - Population Division 2013): in the U.S., 13.7% of the population was 65 y and older in 2012, and this percentage is projected to grow to 16.8% in 2020.

Because of these considerations, data from studies in persons with lesser degrees of renal dysfunction are discussed in the white paper together with data from studies in the general healthy population (although the distinction between the 2 populations and sets of data are preserved). Data from studies in persons with more severe degrees of renal dysfunction, in particular those receiving renal replacement therapy, are discussed only in this section.

Trachtman and others (1995) studied the relationship between dietary intake, race (black compared with white), and BP in children with chronic renal insufficiency (GFR between 20 and 75 mL/min/1.73 m^2). The nutritional data from 118 children (age 18 mo to 10 y) was obtained from the Growth Failure in Children with Renal Diseases Clinical Trial. Mean dietary intakes across all subjects were as follows: calcium 655 ± 254 mg/d, phosphorus 810 ± 292 mg/d, and sodium 1671 ± 727 mg/d. There were no differences between white and black children in mean calcium, phosphorus, or sodium intake. The mean serum calcium concentration for all subjects was within the normal range, with no correlation between the dietary intake of calcium and the serum calcium concentration. There was also no difference in the mean serum calcium or PTH concentrations between the white and black children. Mean systolic and diastolic BPs for all subjects was normal, with no statistically significant difference between white (104 ± 14/69 ± 13 mm Hg) and black (106 ± 12/69 ± 12 mm Hg) subjects. BP was not related to sodium intake or GFR among any group of subjects. Among the entire study group, the systolic ($P = 0.022$) and diastolic ($P = 0.001$) BPs were related to the mean daily phosphorus intake but were unrelated to calcium intake ($P = 0.540$ and $P = 0.223$, respectively). Dietary phosphorus intake was directly related in white children with diastolic BP ($P = 0.011$), while in black children, it was related to both systolic ($P = 0.011$) and diastolic ($P = 0.115$) BPs. Dietary calcium intake was only related among the black children to both systolic ($P = 0.009$) and diastolic ($P = 0.117$) BPs. There was a direct relationship between serum PTH concentrations and systolic and diastolic BPs in the entire study group ($P = 0.017$ and $P = 0.001$, respectively). White children were the only subjects who showed a direct relationship between serum PTH concentrations and diastolic BPs ($P = 0.003$). There was also an inverse relationship between serum calcium concentration and systolic and diastolic BPs in black children. The results from this study demonstrated that in children with renal insufficiency, phosphorus intake was associated with differences in systolic and diastolic BPs and that the associations were different in white and black children.

A1.2.1.1 Serum phosphorus and risk of developing chronic kidney disease. O'Seaghdha and others analyzed data from 2 prospective population-based cohort studies to determine whether serum phosphorus levels were associated with increased risk of incident CKD in the FHS or ESRD (in the NHANES III) (O'Seaghdha and others 2011).

In the analysis of data from the FHS, 2269 subjects were included. Serum phosphorus was measured at the 2nd examination cycle (1978 to 1981) using a standard colorimetric method, and an 8th examination cycle (2005 to 2008) determined eGFR and assessed the development of CKD. The median follow-up was 25.1 y. The mean age was 42 y, and 53.2% were women. Serum phosphorus levels were higher in women ($P < 0.0001$), current smokers ($P < 0.001$), and those with a lower BMI ($P = 0.04$). There was a negative correlation between phosphorus levels and BMI, systolic BP, serum glucose, and high-density lipoprotein (HDL). There was a direct correlation between serum phosphorus levels and eGFR ($r = 0.06$; $P = 0.002$). Incident CKD developed in 267 (11.7%) FHS subjects during follow-up. Subjects in the highest serum phosphorus category (≥4 mg/dL) had an increased risk of incident CKD compared with the referent group in age, sex, and eGFR-adjusted analyses ($P = 0.026$). When analyses were repeated excluding subjects with prevalent CVD, the association of serum phosphorus levels with increased risk of CKD was similar ($P = 0.058$). Dietary information was not available for subjects and cannot be excluded as a confounding variable. The subjects who participated in the FHS were predominantly of European ancestry. Overall, based on the analysis of data from the FHS, O'Seaghdha and others concluded that serum phosphorus levels in the high-normal range are associated with a 2-fold higher risk of developing new onset CKD in the general population.

In the analysis of the NHANES III, 13372 subjects were included. Participants had serum phosphorus measured using an analyzer and vital status information available at follow-up (1988 to 1994). The median follow-up was 9.1 y. The mean age was 44.3 y, and 52% were women. Subjects with serum phosphorus levels of 4 mg/dL or higher, were more likely to be females, Mexican-American, have baseline CKD, use cholesterol-lowering medication, have lower hemoglobin concentration, have higher serum calcium concentration, and have a higher serum HDL cholesterol concentration. During a median follow-up of 9.1 y, 65 NHANES III subjects developed ESRD. Subjects with baseline serum phosphorus levels of 4 mg/dL or more had an increased risk of ESRD in both age-, sex-, and race-/ethnicity-adjusted ($P = 0.007$) and multivariable-adjusted analyses ($P = 0.04$) when compared with subjects having baseline phosphorus level less than 4 mg/dL; it is unclear if baseline renal function was taken into account. When serum phosphorus was analyzed as a continuous variable, an increased risk for ESRD associated with higher serum phosphorus concentration was also observed ($P = 0.002$). When analyses were repeated excluding subjects with prevalent CVD, the RR for incident ESRD was reduced in subjects with serum phosphorus level ≥4 mg/dL as compared with those with level <4 mg/dL ($P = 0.41$). Data were not available to identify incident cases of CKD. Overall, using results of the NHANES III, O'Seaghdha and others concluded that serum phosphorus levels in the high-normal range are associated with a 2-fold higher risk of developing ESRD in the general population.

A1.2.1.2 Normal kidney function to moderate chronic kidney disease. As discussed in Appendix A1.2.1, an estimated 13% of the U.S. population have Stages 1 through 3 CKD; less than 10% of this population were aware of their condition (National Health and Nutrition Examination Survey (a)). The development of CKD is considered part of the aging process (Meyers 2015). Consequently, data and conclusions presented for subjects with normal kidney

function to moderate CKD can be extrapolated to the general population.

In 3 studies, authors discussed the effects of serum phosphorus in subjects with mild to moderate CKD (mean eGFR: >70 mL/min/1.73 m^2) (Ix and others 2009; Murtaugh and others 2012; Palomino and others 2013).

Murtaugh and others (2012) reported a prospective cohort study examining the association between total dietary phosphorus intake and mortality in 1105 adults with early-stage III CKD selected from the NHANES III cohort (refer to the description of study design in Section "All cause mortality"). After adjusting for demographics, comorbidity, eGFR, physical activity, energy intake, and nutritional variables, phosphorus intake was not associated with mortality (HR = 0.98 per 100 mg/dL increase in phosphorus intake, 95% CI: 0.93 to 1.03). Additionally, after adjusting for demographics, calorie intake, percent calories from protein intake, time of blood draw, and duration of fasting, a 100 mg/dL increase in dietary phosphorus was associated with a change in serum phosphorus of 0.009 mg/dL (95% CI: 0.006 to 0.011 mg/dL). In the authors' opinion, these results suggest that, in early-Stage 3 CKD, higher dietary phosphorus intake is associated with a very modest increase in serum phosphorus concentration but not with an increase in mortality.

In a prospective observational study, Palomino and others (2013) followed 880 subjects with stable CVD and normal kidney function or mild-to-moderate CKD for a median of 7.4 y and monitored for cardiovascular events and all-cause mortality. Serum phosphorus concentration and 24-h urine phosphorus excretion were measured at baseline. Mean age was 67 ± 11 y, mean eGFR was 71 ± 22 mL/min/1.73 m^2, and mean serum phosphorus was 3.7 ± 0.6 mg/dL. There was no statistically significant association of urine phosphorus excretion with all-cause mortality irrespective of kidney function.

In a cross-sectional study, Ix and others (2009) found the associations of serum phosphorus with ABI, pulse pressure, and large and small artery elasticity among 1370 subjects (440 subjects with moderate CKD, eGFR <60 mL/min/1.73 m^2). The mean age was 64 ± 10 y and 55% of subjects were female. A total of 39% were white, 27% were black, 20% were Hispanic, and 14% were Chinese. The mean serum phosphorus concentration was 3.5 ± 0.5 mg/dL, and the mean eGFR was 71 ± 19 mL/min/1.73 m^2. The associations between serum phosphorus concentrations and high ABI were similar among subjects with or without CKD (P = 0.88). The associations between serum phosphorus concentrations and each continuous measure of stiffness were similar among subjects with or without CKD. Further discussion of variables related to CVD is provided in Appendix A1.2.2.

A1.2.1.3 Moderate to severe chronic kidney disease. Several primary studies determined the effects of a phosphorus restricted (Barsotti and others 1998; Newsome and others 2013; Goto and others 2014), a phosphorus-supplemented (Muras and others 2013), or a standard diet (Moe and others 2011; Houston and others 2013; Moore and others 2015) in subjects with moderate to severe CKD. In one study, the authors compared the effects of all 3 diets in subjects with CKD (Ix and others 2014). In 2 studies, the authors examined dietary phosphorus intake in patients on hemodialysis (Noori and others 2010a, 2010b; Lynch and others 2011).

The following 3 studies evaluated the effects of phosphorus restriction on serum phosphorus and hormone levels in subjects with moderate to severe CKD. Newsome and others (2013) conducted a *post hoc* analysis of the Modification of Diet in Renal Disease Study to determine the effects of dietary protein restriction on serum and urine phosphate levels. The Modification of Diet in Renal Disease Study consisted of 2 studies with 3 y of follow-up. In Study A, patients were randomly assigned to receive a usual-protein or low-protein diet (n = 585; GFR: 25 to 55 mL/min/1.73 m^2). In Study B, patients were randomly assigned to receive a low-protein or very low-protein diet with ketoacids (n = 255; GFR: 13 to 24 mL/min/1.73 m^2). For the usual-protein diet, the phosphorus content was 16 to 20 mg/kg/d. For the low-protein diet, the phosphorus content was 5 to 10 mg/kg/d. For the very low-protein diet, the phosphorus content was 4 to 9 mg/kg/d. The mean age was 52 ± 12 y. In Study A, the mean change in serum phosphate levels between months 0 and 4 for patients on the usual-protein diet was 0.01 mg/dL (95% CI: 0.05 to 0.06) and for patients on the low-protein diet was 0.05 mg/dL (95% CI: –0.10 to 0.01 mg/dL). In Study B, the mean change in serum phosphate levels between months 0 and 4 for patients on the low-protein diet was −0.17 mg/dL (95% CI: –0.29 to –0.04 mg/dL) and for patients on the very low-protein diet was –0.25 mg/dL (95% CI: −0.38 to 0.12 mg/dL). Overall, dietary protein restriction resulted in a modest but sustained decrease in serum phosphate levels (Newsome and others 2013).

Goto and others (2014) noted that elevated FGF-23 levels were associated with disease progression in patients with CKD. The study evaluated the effects of a standard low-protein diet on serum FGF-23, iPTH, and 1,25$(OH)_2$D in patients with early and advanced CKD. This study is also summarized in Section "Other associations and analyses" of the white paper. While the findings in the early CKD group are relevant to Appendix A1.2.1.2, the Goto and others study is presented in this section because of specific findings within the advanced CKD group. Early CKD is defined as an eGFR of 60 mL/min/1.73 m^2 or greater and proteinuria or hematuria for at least 3 mo; advanced CKD is defined as an eGFR less than 30 mL/min/1.73 m^2 for at least 3 mo. All participants consumed a regular diet (15 to 20 mg/kg/d of phosphorus) for 2 d, followed by a low-protein diet (10 to 15 mg/kg/d of phosphorus) for 4 to 6 d. Fasting blood samples and 24-h urine samples were collected on the final day of each diet regimen. A total of 35 subjects were included in the final analysis. It is important to note that in the advanced CKD group, subjects were significantly older and included a higher percentage of males than in the early CKD group. In addition, 45% of subjects in the advanced CKD group had diabetes as compared with no patients in the early CKD group. Serum FGF-23 levels significantly decreased in both groups after the low-protein diet regimen (early CKD, from 52.8 to 38.6 pg/mL, P = 0.006; advanced CKD, from 185.4 to 138.2 pg/mL, P = 0.005). Serum PTH levels significantly decreased in the advanced CKD group (123.5 to 85.0 pg/mL, P = 0.001), with no significant change in the early CKD group. Serum 1,25D$(OH)_2$D levels significantly increased in the early CKD group (36.0 to 47.0 pg/mL, P = 0.03). Serum calcium levels were unchanged in both groups, while serum phosphorus levels had a statistically significant decrease in the advanced CKD group only. Urinary phosphorus levels had a statistically significant decrease in both groups. There was a significant correlation between changes in serum FGF-23 and urinary phosphorus excretion in the advanced CKD group (r = 0.46; P = 0.04). Overall, short-term consumption of a low-protein diet decreased serum FGF-23 levels in patients with CKD.

A prospective interventional trial evaluated the effects of a very low-protein, low-phosphorus diet supplemented with essential amino acids, keto analogs, and calcium carbonate, on circulating levels of iparathyroid hormone in severe chronic renal failure

patients (defined as serum creatinine >6.5 mg/dL) with secondary hyperparathyroidism, who were not treated with any vitamin D preparations (Barsotti and others 1998). A total of 21 patients with chronic uremia (12 males, 9 females) were enrolled. At entry, all patients were following a standard low-protein diet (0.6 g/kg/d of protein and 9 to 10 mg/kg/d of phosphorus). A diet was administered that consisted of a very low protein (0.3 g/kg/d) and very low phosphorus (5 mg/kg/d), supplemented with a mixture of essential amino acids and calcium keto analogues (Keto diet). Calcium carbonate (2 to 4 g/d), iron, and vitamin B12 preparations were also administered. After 4 mo, there were statistically significant changes in several key laboratory parameters. Mean iPTH serum levels decreased by 48%, from a mean of 441 to 225 pg/mL ($P < 0.001$). Plasma phosphorus decreased (5 to 3.7 mg/dL; $P < 0.001$), calcium increased (8.3 to 8.9 mg/dL; $P < 0.001$), creatinine clearance decreased (7.2 to 5.6 mL/min; $P < 0.001$), and protein catabolic rate was reduced. The results demonstrated that reducing dietary phosphorus resulted in significantly reduced iPTH serum levels in patients with severe chronic renal failure who also have secondary hyperparathyroidism.

A prospective interventional study evaluated changes in serum calcium and phosphorus concentrations and in physiologically related parameters after consumption of a phosphorus-supplemented diet by DM and non-DM patients with impaired kidney function (Muras and others 2013). The study evaluated the effects of a 6-d high-phosphate diet (1800 mg/d) on serum FGF-23 and other parameters of calcium and phosphate metabolism. Subjects with Stage 3 to 5 CKD (eGFR <60 mL/min/1.73 m^2) and albuminuria less than 300 mg/g creatinine were enrolled. All DM patients had a confirmed diagnosis of Type 2 DM. Subjects received a normal phosphate diet (700 ± 100 mg/d) for the 7 d preceding the study; the diet was prescribed and supervised by a registered dietitian. A high-phosphate diet was administered for 6 d and was supplemented with 100 mL of sodium and potassium phosphate solution. The total phosphorus (TP) intake was 1800 mg/d. Baseline, day 3, and day 7 serum FGF-23, PTH, calcium, phosphorus, 25-OHD, $1,25(OH)_2D$, monocyte chemoattractant protein-1 concentrations, and calcium and phosphate urine excretion were measured. Serum PTH and FGF-23 increased after consumption of the high-phosphate diet in both DM and non-DM patients. However, the changes of serum FGF-23 between baseline and day 7 in non-DM patients tended to be higher than in diabetic patients. Muras and others concluded that FGF-23 secretion was impaired after phosphate load in DM patients with Stage 3 to 5 CKD but not in non-DM patients with similar renal dysfunction. In addition, although FGF-23 secretion was impaired in DM patients, serum phosphate concentration did not increase significantly, and there was no significant change in urine phosphate during phosphate intake. The results indicated that in non-DM patients, there was not a significant decrease of serum calcium concentration, and serum PTH remained almost constant during the high-phosphate diet. The authors noted that the more pronounced FGF-23 response to a high phosphate intake in subjects with non-DM CKD suggests an inhibition of PTH secretion by high FGF-23 secretion.

In the following studies, authors determined the effects of dietary phosphorus on serum phosphorus and hormone levels in subjects with moderate to severe CKD. Moore and others (2015) conducted a cross-sectional analysis of serum phosphorus concentrations compared with clinical characteristics and dietary intake reported 24 h before blood analysis. Data were extracted from the NHANES, 2003 to 2006. A detailed description of this study is presented in Section "Food-additive phosphate and serum phosphorus concentration" of the white paper. Of the 7895 participants of this study, 0.8% had an eGFR less than 30, 3.7% had an eGFR of 30 to 44, 13.4% had an eGFR of 45 to 59, 19.8% had an eGFR of 60 to 74, 18.4% had an eGFR of 75 to 89, 22.7% had an eGFR of 90 to 105, and 21.2% had an eGFR greater than 105 mL/min/1.73 m^2. Participants with a low eGFR (<30 mL/min/1.73 m^2) had significantly higher serum phosphorus levels (4.12 ± 0.07 mg/dL, $P = 0.0009$) than the reference group (≥105 mL/min/1.73 m^2, 3.83 ± 0.02 mg/dL). In addition, having a dietary intake of foods with inorganic phosphates ($r = 0.064$, $P < 0.0001$) and food containing organic phosphates ($r = 0.075$, $P = 0.024$) correlated with serum phosphorus concentration.

Houston and others (2013) performed a cross-sectional analysis of 74 CKD patients not yet requiring hemodialysis to determine if markers of phosphorus metabolism were associated with increased arterial stiffness (measured by augmentation index) in kidney disease. The study included adults with Stage 3 or 4 CKD (eGFR: 15 to 59 mL/min/1.73 m^2 for more than 3 mo). The authors detected no associations of serum phosphorus, urinary phosphate excretion, estimated daily phosphorus intake, or FGF-23 with vascular stiffness, assessed as augmentation index. There was no significant difference in serum phosphate concentrations across stages of kidney function. Urinary phosphate excretion decreased as creatinine clearance decreased. Plasma FGF-23 levels were directly associated with serum phosphate levels ($r = 0.24$; $P = 0.03$) and inversely correlated with creatinine clearance ($r = –0.4$, $P = 0.001$); there was no association with daily phosphorus intake or with urinary phosphate excretion.

Moe and others (2011) conducted a crossover trial to compare the effects of vegetarian and meat diets on phosphorus metabolism and hormonal changes in subjects with CKD. Both diets contained 2200 kcal, 1000 mg calcium, 3000 mg sodium, and 800 mg phosphorus per day. The phosphorus content in diets was confirmed photometrically. A total of 8 subjects (4 men, 4 women) completed both arms of the study and were included for analysis. At baseline, the mean age was 61 ± 8.4 y, mean eGFR was 32.3 ± 6 mL/min, and mean BMI was 32 ± 5. Subjects were randomized to initially receive a grain-/soy-based protein diet (referred to as vegetarian) or a meat-/dairy-based protein diet (referred to as meat) for 7 d. During the last 24-h period of each diet, blood and urine were collected 30 min after each of the 3 meals. After a washout period of 2 to 4 wk, subjects received the alternative diet and study procedures were repeated. There was no carryover effect between each treatment arm. Urinary phosphorus excretion was greater in the meat diet group, although it did not reach significance ($P = 0.07$). There was no difference in plasma sodium, calcium, or creatinine levels or 24-h urine sodium, calcium, or nitrogen concentrations between the 2 diets. However, there was a trend for decreased urine pH and ammonium excretion in the meat (pH 6.6 ± 0.7, ammonium 5.6 ± 2.8 mmol/d) compared with vegetarian diet (pH 7.0 ± 0.6, $P = 0.2$; ammonium: 9.9 ± 6.4 mmol/d, $P = 0.07$). There was a significant correlation between the change in plasma phosphorus concentration and the change in FGF-23 ($r = 0.54$; $P = 0.03$), but no relationship with 25-hydroxyvitamin D, 1,25D, or PTH levels. There was significantly greater FEP (24% compared with 18%; $P = 0.0001$) and significantly lower PTH (44 pg/mL compared with 52 pg/mL; $P = 0.0002$) after consuming the meat-based diet compared with the vegetarian diet. After consuming the meat-based diet, subjects had overall greater calcium plasma levels (9.1 mg/dL) compared with the vegetarian diet

(8.8 mg/dL; $P = 0.0001$). Moe and others indicated that despite equivalent protein and phosphorus concentrations in both diets, subjects had lower plasma phosphorus levels, decreased urine 24-h phosphorus excretion, and significantly decreased FGF-23 levels on the vegetarian diet compared with the meat-based diet.

A crossover feeding study evaluated the circadian pattern of serum phosphate concentrations in 11 subjects with CKD (eGFR: 30 to 45 mL/min/1.73 m^2) after consumption of a high-, standard-, and low-phosphate diet (Ix and others 2014). This study is summarized in Section "Total dietary phosphorus and serum phosphorus concentration" of the white paper. Overall, a circadian pattern of serum phosphorus was observed in CKD that could be modified by phosphorus intake.

Noori and others (2010a) reported a prospective cohort study examining the association of dietary phosphorus intake and phosphorus-to-protein ratio with mortality in patients on maintenance hemodialysis. The study was conducted in 224 of the 1300 participants in the Nutritional and Inflammatory Evaluation in Dialysis study. The maximum follow-up time was 5.25 y, and 81 patients (36%) died during the study. After adjustment for the specified covariates, the HR for death for participants in the highest tertile of dietary phosphorus intake relative to those in the lowest tertile was 2.59 (95% CI: 1.10 to 6.08: $P = 0.03$ for trend across all tertiles); the HR for death for participants in the highest category of dietary phosphorus-to-protein intake ratio relative to those in the reference (2nd-lowest) category was 2.09 (95% CI: 1.08 to 4.05; $P = 0.02$ for trend across all 4 categories).

Lynch and others (2011) conducted a *post hoc* analysis of data from the hemodialysis study to determine the long-term effects of prescribed dietary phosphate restriction on patient survival. A total of 1751 hemodialysis patients (of 1846) from the Hemodialysis Study had sufficient data for inclusion in this analysis. Patients were enrolled between March 1995 and October 2000, and follow-up continued through the end of 2001. Prescribed daily phosphate was restricted to levels of 870 mg or less ($n = 300$), 871 to 999 mg ($n = 314$), 1000 mg ($n = 307$), 1001 to 2000 mg ($n = 297$), and unrestricted ($n = 533$). There was no consistent trend in serum phosphate or corrected calcium levels across the prescribed daily phosphate quantities, but patients on more restrictive prescribed daily phosphate had higher PTH levels. Compared with patients on the most restrictive prescribed daily phosphate regimen (≤870 mg), patients in the 1001- to 2000-mg/d group (HR: 0.73 [95% CI: 0.54 to 0.97]) and unrestricted group (HR: 0.71 [95% CI: 0.55 to 0.92]) were associated with statistically significant reductions in all-cause mortality as determined by the marginal structural analysis.

A1.2.1.4 Summary. The following summarizes the associations of serum phosphorus in individuals with mild to severe kidney disease. In diets restricting phosphorus, authors reported sustained decreases in serum phosphorus, FGF-23, and PTH in subjects with CKD (Barsotti and others 1998; Newsome and others 2013; Goto and others 2014). Muras and others (2013) reported that in phosphorus-supplemented diets, FGF-23 and PTH increased in subjects with CKD, regardless of an individual's diabetic status. In DM subjects with CKD, urine phosphorus excretion increased during phosphorus supplementation. In non-DM subjects with CKD, serum phosphorus increased during phosphorus supplementation. Houston and others (2013) found that FGF-23 correlated with serum phosphorus, but there was no association with daily phosphorus intake or urinary phosphorus excretion. Interestingly, Moe and others (2011) determined that subjects with CKD who consumed a vegetarian diet had lower serum phosphorus levels, lower urinary phosphorus excretion, and lower FGF-23 than while consuming a meat-based diet, despite equivalent protein and phosphorus concentrations in both diets.

Limitations of these studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake in the general population include the limited utility of findings from studies in diseased subpopulations, especially those with diseases such as CKD, to draw conclusions regarding the general healthy population; and the limited reliability of the methods used for quantification of dietary phosphorus intake. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.2.2 Cardiovascular disease. A review of the literature identified 6 studies that evaluated the association of dietary phosphorus with manifestations or biomarkers of CVD; one of the studies evaluated the association of food-additive phosphate (AP) and CVD. In addition, 9 studies evaluated the association of serum phosphorus concentrations with CVD (study details are provided in Section "Serum phosphorus concentration and clinical outcomes" of the white paper).

A statistically significant association was noted between higher dietary phosphorus density and increased cardiovascular mortality in 9686 healthy, nonpregnant adults, aged 20 through 80 y, selected from the NHANES III (Chang and others 2014). However, there was no association between absolute phosphorus intake and cardiovascular mortality (study details are provided in Section "Total dietary phosphorus and clinical outcomes" of the white paper).

Kwak and others (2014) evaluated 23652 healthy Korean adults (age: 40.8 ± 7.3 y) in a cross-sectional study that assessed whether dietary calcium and phosphorus intakes and serum concentrations were associated with the prevalence of CAC in subjects without a history of CKD or CVD. The study design is described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper. CAC score ratios reflected the degree of CAC. There was no association between dietary phosphorus or dietary calcium intake with CAC score ratios. However, serum calcium and phosphorus concentrations and CP-Ps were significantly associated with the CAC score ratios. High serum calcium and phosphorus concentrations and high calcium-phosphorus products were associated with an increased prevalence of CAC regardless of serum vitamin D levels.

An analysis of 4494 subjects (mean age: 61.6 y) with no baseline CVD, drawn from the MESA study evaluated the association of dietary phosphorus with changes in LVM (Yamamoto and others 2013). Details of the study are described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper. After adjusting for height, weight, age, and race, each 20% greater estimated dietary phosphorus intake was associated with an estimated 0.42 g greater LVM (95% CI: 0.14 to 0.70 g) and with a higher mass-to-volume ratio (0.006 g/mL; $P = 0.02$), but not with differences in left ventricular end-diastolic volume or stroke volume. After adjusting differences in sex, higher estimated dietary phosphorus was associated with greater LVM, which was stronger among women (particularly postmenopausal women) than men.

A cross-sectional analysis of 74 patients with Stage 3 or 4 CKD who did not require hemodialysis determined if markers of phosphorus metabolism were associated with increased arterial stiffness in kidney disease (Houston and others 2013). Augmentation index was measured in the study and is considered a validated surrogate marker of arterial stiffness; an elevated augmentation index has been shown to be an independent marker of morbidity and

mortality in patients with CKD. There were no associations of serum phosphate, urinary phosphate excretion, estimated daily phosphorus intake or FGF-23 with augmentation index. However, the results indicated that older age, black race, and higher BP were independent predictors of greater arterial stiffness in CKD.

A cross-sectional analysis of healthy adults randomly selected from the Population Register Centre in Finland evaluated whether dietary phosphorus intake (TP, food-additive phosphate, or eTP) is associated with higher carotid IMT and whether high dietary phosphorus intake is a CVD risk factor in a general population (Itkonen and others 2013). The study evaluated 546 adults (176 males and 370 females), average age of 41.9 y, from Finland, and is described in Section "Food-additive phosphate, target organs, and biomarkers" of the white paper. The analysis of data across all subjects in the study demonstrated no statistically significant association between TP or food-additive phosphate intake and IMT. In the subgroup consisting of females, however, a statistically significant difference in IMT between the highest and lowest quintiles of TP intake was demonstrated ($P = 0.035$), with higher TP being associated with higher IMT. This association was apparent for females also when quintiles of eTP intake were used in the analysis. In similar comparisons in males, there was no statistically significant difference observed. In summary, based on an analysis of grouped data from all subjects, there was no statistically significant association between TP, eTP, or food-additive phosphate with IMT.

The study reported no statistically significant association between TP or food-additive phosphate intake and IMT ($P > 0.05$, ANCOVA). There was, however, a significant positive linear trend between energy-adjusted TP intake and IMT ($P = 0.039$) and between FAP intake and IMT ($P = 0.022$). The authors concluded that dietary P intake should be further investigated due to its potential association with adverse cardiovascular health effects.

A cross-sectional study in the United States evaluated the association of dietary phosphorus intake with BP and risk of hypertension in 13444 subjects (from the ARIC and MESA studies; age range: 45 to 64 y) (Alonso and others 2010). The study is described in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper. The results in both studies demonstrated that, after adjustment of potential confounders, including BMI, smoking, physical activity, and eGFR, higher phosphorus intake was statistically significantly associated with lower levels of systolic and diastolic BP. During an average follow-up of 6.2 y (7.1 y in ARIC, 3.8 y in MESA), 3345 incident cases of hypertension (2400 in ARIC, 945 in MESA) were identified. Individuals in the top quintile of phosphorus intake had approximately a 10% lower risk of hypertension than those in the lowest quintile of phosphorus intake, after adjustment for potential confounders. An increase in phosphorus intake was associated with a lower risk of hypertension in both men and women. While dietary phosphate was obtained from different sources, including meat and grain, only higher phosphorus intake from dairy products, not other dietary sources, was associated with lower levels of systolic BP and lower risk of hypertension.

The association of total dietary phosphorus and BP was evaluated in the International Study of Macro- and Micro-Nutrients and Blood Pressure, which was a cross-sectional epidemiologic study of 4680 men and women (age: 40 to 59 y) from 17 population samples in Japan, China, the United Kingdom, and the United States (Elliott and others 2008). Dietary intakes were obtained from four 24-h recalls plus data on supplement use; 5 food groups contributed most of the dietary phosphorus in each country (65% to 81%). In the study, the main dietary sources of phosphorus were milk, cheese, meats, and poultry in the Western diets and pasta, rice, noodles, fish, and shellfish in the Chinese and Japanese diets. Mean systolic BP ranged from 117.2 (Japan) to 121.3 mm Hg (China), mean diastolic BP ranged from 73.2 (China) to 77.3 mm Hg (the U.K.), and mean dietary phosphorus intake ranged from 439 mg/1000 kcal (of China) to 662 mg/1000 kcal (the U.K.). All the associations of energy-corrected total dietary phosphorus intake with BP were inverse. Estimates of the changes in BP ranged from −1.13 to −2.31 mm Hg for systolic BP and −0.59 to −1.47 mm Hg for diastolic BP per +232 mg/1000 kcal (equal to 2 SDs) of phosphorus intake. The authors noted that high intercorrelations with other minerals, especially calcium, limited the ability to assign a possible BP-lowering association to serum phosphorus concentration itself.

The results from 9 studies indicated that serum phosphorus concentrations were associated with various manifestations of CVD (described further in Section "Serum phosphorus concentration and clinical outcomes" of the white paper). High serum phosphorus concentrations were associated with incident cardiovascular events and with heart failure in healthy individuals (Dhingra and others 2007; Foley and others 2008; Larsson and others 2010), with all-cause and cardiovascular mortality (Chang and Grams 2014) and with increased risk of death and cardiovascular events in people with CVD or prior MI (Tonelli and others 2005; Dhingra and others 2010). Another study found that high serum phosphorus levels were associated with high coronary artery calcium, a risk factor for coronary artery atherosclerosis in healthy young adults (Foley and others 2008). However, one study did not find a significant association of serum phosphorus with coronary artery disease and gender in healthy individuals (Onufrak and others 2009), and another study observed no associations between plasma phosphorus levels and risk for incident nonfatal MI or fatal coronary heart disease (CHD) in healthy men (Taylor and others 2011). The results of a cross-sectional analysis indicate that higher serum phosphorus concentrations (>4 mg/dL) were associated with a significantly greater risk of vascular stiffness as indicated by the ABI (Ix and others 2009); other measures of vascular stiffness were statistically significantly associated with increased serum phosphorus levels.

In summary, only one published study evaluated the association of AP with cardiovascular morbidity: a cross-sectional analysis reported no statistically significant association between dietary phosphorus or AP and carotid IMT in all subjects evaluated, but various subgroup analyses did identify some associations between dietary phosphorus and IMT (Itkonen and others 2013). Most studies demonstrated no association of dietary phosphorus with either biomarkers or manifestations of CVD. Two studies that evaluated the association of dietary phosphorus and changes in BP reported either an inverse relationship of dietary phosphorus with BP or an increase in phosphorus intake was associated with a lower risk of hypertension in both men and women (Elliott and others 2008; Alonso and others 2010). A study in patients with Stage 3 or 4 CKD showed no associations of serum phosphate, urinary phosphate excretion, estimated daily phosphorus intake, or FGF-23 with augmentation index, a surrogate marker of arterial stiffness (Houston and others 2013). Another study showed no association between absolute phosphorus intake and cardiovascular mortality (Chang and others 2014). A study indicated no association between dietary phosphorus or dietary calcium intake with CAC score ratios but did find that high serum calcium and phosphorus concentrations and high calcium-phosphorus products were

associated with an increased prevalence of CAC regardless of serum vitamin D (Kwak and others 2014).

Two additional studies evaluated dietary phosphorus: one study reported no association between absolute phosphorus intake and cardiovascular mortality (Chang and others 2014), and one study reported that phosphorus intake was associated with lower BP (Elliott and others 2008).

In most of the 9 studies that evaluated serum phosphorus levels and CVD, high serum phosphorus concentrations were associated with increased CVD and death. High serum phosphorus concentrations were associated with increased risks of incident CVD and heart failure in 3 studies in subjects with no baseline CVD (Dhingra and others 2007; Foley and others 2008; Larsson and others 2010), increased vascular stiffness in one study (Ix and others 2009), and with increased risk of death and cardiovascular events in individuals with prior MI or CVD in 2 studies (Tonelli and others 2005; Dhingra and others 2010). In addition, increased mortality was associated with high serum phosphorus concentrations in subjects with no history of CVD in 3 studies (Onufrak and others 2009; Larsson and others 2010; Chang and Grams 2014). However, one study reported no association of serum phosphorus levels with cardiovascular events or cardiovascular deaths (Taylor and others 2011). In the studies that evaluated serum phosphorus levels and cardiovascular risks, there were no measures of total dietary or food-additive intake of phosphorus so the association of dietary phosphorus with risk of CVD in these studies was not assessed.

None of these studies were prospective, randomized, controlled studies, and most were analyses of observational cohorts. The quality of evidence from these noninterventional studies is low based on the evaluation of the quality of evidence (Appendix C), and no direct causal relationships can be inferred. The studies were of several different designs, and the inherent limitations of these designs in allowing the studies to contribute to the assessment of the risks or safety of various levels of dietary phosphorus intake, as well as other limitations relevant to these studies, are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.2.3 Bone health. A total of 26 articles spanning all age ranges assessed the associations between phosphorus and bone health. Narrative summaries are provided below, and a summary of the study objectives and design is presented in Table A7. All the studies are presented in more detail in other sections of the white paper.

The associations of dietary phosphorus in a well-nourished population during the last trimester of pregnancy with bone density of offspring in childhood and adolescence is addressed in 2 articles drawing subjects from the same birth cohort in Tasmania, Australia. These data are presented in Appendix A1.2.5, and summaries of the studies are included in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper.

Three studies evaluated bone mineral density in children and the associations with phosphorus, either as total dietary intake or as cola beverages. These data are presented in Appendix A1.1.1.

In contrast to the abundance of studies in women, only one study assessed markers of calcium and bone metabolism in young men. Kristensen and others (2005) investigated the effects of administering Coca Cola or milk in 2 sequential intervention periods each lasting 10 d. This study is summarized in Section "Food-additive phosphate, target organs, and biomarkers" of the white paper. While serum calcium levels remained unchanged, serum phosphorus levels rose significantly in the cola period. Markers of bone resorption, osteocalcin, parathyroid hormone, and $1,25(OH)_2D$ rose during the cola period suggesting an increase in bone turnover rate. The authors suggest that the changes were due to the low calcium-to-phosphorus intake ratio during the cola period in comparison to the milk period, and that the calcium-to-phosphorus ratio in the diet is of greater significance than absolute (energy adjusted) phosphorus intake. Both absolute calcium and phosphorus intakes, as well as the calcium-to-phosphorus intake ratio, were much higher during the milk period than the cola period.

A Korean study determined that, phosphorus intake was significantly correlated with the following: lumbar BMD in men younger than 50 y and in postmenopausal women; femoral neck BMD in postmenopausal women and in men 50 y and older; and total body BMD in men 50 y and older (Lee and others 2014). After adjusting for confounding factors using 3 different models, dietary calcium and calcium-to-phosphorus ratio were positively associated with BMD in the femoral neck in men aged 50 y and older. In premenopausal women, only calcium intake was associated with total body BMD. No association was detected between phosphorus intake and BMD in any skeletal region. The mean calcium-to-phosphorus intake ratios in these men (0.4) and women (0.41) were relatively low. This study is summarized in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper.

Low phosphorus and zinc intakes were associated with an increase in fracture risk in middle-aged and elderly Swedish men after an adjustment for age, energy intake, and previous fracture (Elmståhl and others 1998). A summary of this article is included in Section "Bone health" of the white paper. Of note, phosphorus intakes in the lowest decentile were 1347 mg/d, almost double the recommended daily allowance in Sweden, and calcium intakes were above 800 mg/d in 80% of the men. The authors noted that no dose–response relationship was present for phosphorus, possibly due to a threshold effect. A high dietary fat intake was also associated with an increase in fracture risk.

Trautvetter and others conducted an 8-wk randomized, placebo controlled trial to investigate the impact of 2 doses of a calcium supplement on calcium, phosphorus, magnesium, and iron metabolism in healthy adults, each of whom also received a 1000-mg phosphate supplement per day (Trautvetter and others 2016). The study design is described in Section "Association of phosphorus load with regulatory hormones and other physiological outcomes" of the white paper. Results were compared across each arm for the different sampling time points, and differences were also compared across study arms. In the calcium-supplemented arms (1000 and 500 mg/d), serum levels of bone formation and bone resorption markers decreased. Compared with placebo, osteocalcin decreased significantly after 8 wk, while BALP was decreased significantly at 4 wk for both calcium-supplemented arms, and at 8 wk for the 1000-mg calcium arm only. The marker of bone resorption, C-telopeptides, was decreased in both calcium-supplemented arms after 8 wk and was also decreased at 4 wk in the 1000-mg calcium arm. Significant effects of the various calcium doses on urinary calcium excretion were also noted. The authors conclude that a high phosphate intake, without adequate calcium intake, has a negative effect on calcium metabolism and that an adequate calcium-to-phosphorus intake ratio is important for normal calcium metabolism.

In summary, of the 26 articles included in this section, 5 examined the associations between cola intake and bone health and 4 of these reported adverse associations, including increased

Table A7–Studies assessing relationship between phosphorus and bone health

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Kärkkäinen and Lamberg-Allardt (1996)	10 women in Part 1 10 women in Part 2 Age 21 to 34 y	Supplement • Part 1: single dose of 1500 mg phosphorus in water, or placebo • Part 2: 3 doses of phosphorus (500 mg each) in water, or placebo	Randomized, controlled study	• Markers of Ca and bone metabolism were monitored for 24 h after a phosphate supplement was administered in conjunction with a low Ca diet. • Serum P and PTH concentration was increased, and serum Ca was decreased when compared with placebo. Markers of bone formation decreased.
Elmståhl and others (1998)	6576 men Age 46 to 68 y	Total dietary intake, including dietary supplements	Prospective cohort study	• Dietary risk factors for fracture in middle-aged and elderly men living in Malmö, Sweden. • Low P and zinc intakes were associated with an increase in fracture risk in middle-aged and elderly Swedish men.
Teegarden and others (1998)	215 women Age 18 to 31 y	Total dietary intake	Cross-sectional study	• A study of the associations between bone mineral measurements and dietary calcium, protein, and P in young American women. • Positive correlation between intake of protein, Ca, and P with BMD of the radius and spine as well as BMC of the spine.
Brot and others (1999)	510 women Age 45 to 58 y	Total dietary intake	Cross-sectional study	• To determine the relationships between BMD, Vit D metabolites, and Ca:P intake ratio in healthy Danish perimenopausal women. • Ca intake and Ca:P intake ratio were positively associated with BMD and negatively associated with $1,25(OH)_2D$.
Jones and others (2000)	173 boys and girls Age 8 y	Total dietary intake (maternal)	Prospective cohort study	• Maternal dietary intake during last 3 mo of pregnancy and effects on BMD of the offspring at 8 y old. • After adjustments, the only statistically significant associations were between P and fat intakes and lumbar spine BMD. • A child in the ideal exposure categories for K, Mg, P, protein, and fat had a 5% to 12% higher BMD at age 8 y than those without the ideal exposure.
Heaney (2000)	191 women Age 35 to 77 y 567 separate studies over 32 y	Total dietary intake	Prospective cohort study	• To determine whether P or protein intake affect Ca absorption using data from full metabolic balance studies conducted in a cohort of 191 Roman Catholic nuns. • There was no relationship between the relative absorption of Ca and either P or protein intake.
Wyshak (2000)	460 girls Mean age ± SD: 15 y, 8 mo ± 10 mo	Food additive intake (colas)	Cross-sectional study	• Assessment of physical activity, carbonated beverage intake (both cola and noncola), and bone fracture history in high school girls. • In all girls, regardless of physical activity, fracture risk was associated with cola beverage intake when compared to girls who did not consume any cola beverages. In physically active girls, intake of both cola and noncola carbonated beverages was associated with increased fracture risk.
Heaney and Rafferty (2001)	30 women Age 20 to 40 y	Food additive (phosphoric acid-containing cola drinks)	Randomized, controlled study (incomplete random block)	• Impact of various drinks on urinary Ca levels in habitual soft drink consumers was assessed. Study arms included milk as well as soft drinks with and without caffeine, with and without phosphoric acid, and with and without sugar. • Increases in urinary calcium excretion were greater after consuming the 2 caffeine-containing beverages (and greatest for positive control, milk). • No excess calciuria was detected in noncaffeinated, phosphoric acid-containing beverages. Phosphoric acid did not increase the calciuric effects of the caffeinated beverages.
Grimm and others (2001)	10 women Age 23 to 29 y	Supplement	Controlled interventional study	• Markers of Ca and bone metabolism and parameters of renal function monitored during a 6-wk high P period as well as 2 control periods (before and after). • There were no statistically significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption, and renal function during the P-supplemented period.

(*Continued*)

Table A7–Continued.

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Méndez RO and others, 2002	47 women Age 45 to 63 y	Total dietary intake	Cross-sectional analysis	• Associations between dietary P, and Ca intake and excretion, anthropomorphic measures, estradiol level, and BMD in postmenopausal Mexican women. • No association was identified between dietary P or Ca intake and BMD of the heel or forearm.
Heaney and Nordin (2002)	191 women Age 35 to 65 y 88 women and 5 men Age 19 to 78 y	Total dietary intake (including all supplements)	Longitudinal cohort study Cross-sectional study	• Effect of Ca intake on absorption of dietary P using data from full metabolic balance studies conducted in a cohort of 191 Roman Catholic nuns, and at a metabolic research unit in Leeds. • As Ca intake increased without a corresponding increase in P intake, P absorption fell.
Ma and others (2004)	Cases: 206 boys and girls Controls: 206 boys and girls Age 9 to 16 y	Food additive intake (carbonated soft drinks, colas)	Case–control study	• Association between soft drink consumption and upper limb fracture risk and to explore whether effect is mediated through BMD, physical inactivity, and/or milk intake (Hobart, Tasmania). • A statistically significant linear dose–response association between cola soft drink intake and the risk of wrist and forearm fractures were reported in both boys and girls. After adjustment the association was no longer statistically significant. Consumption of cola drinks and other carbonated beverages was associated with television, computer, and video watching, and television, computer, and video watching was reported to be an independent risk factor for wrist and forearm fractures.
Bounds and others (2005)	52 boys and girls Age 6 and 8 y	Total dietary intake	Prospective cohort study	• Association between dietary and lifestyle factors, BMC and BMD. • Longitudinal dietary P intake, as well as other nutritional factors, were positively associated with total BMD and BMC in children at age 8 y.
Kristensen and others (2005)	11 men Age 22 to 29 y	Food additive (cola compared with milk)	Randomized, crossover study	• Impact of 10-d low Ca diet plus either 2.5 L cola or semiskimmed milk on markers of Ca and bone metabolism. • Significant increases in the biochemical markers of bone turnover occurred in the cola arm compared to the milk arm. The study illustrated the potential health risk of inadequately low calcium intake and a low Ca:P ratio.
Tucker and others (2006)	1413 women 1125 men Age 29 to 83 y	Food additive as cola beverages (total dietary intake also assessed)	Cross-sectional study	• Relationship between cola intake (and intake of other carbonated beverages) and BMD in men and women. • Intake of cola (but not of other carbonated soft drinks) is associated with low BMD in women (cola consumers had significantly lower intakes of Ca and lower Ca:P intake ratios for [both total and dietary Ca] than individuals who did not consume colas).
Kemi and others (2006)	15 women Age 20 to 28 y	Supplement	Randomized, crossover study	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate supplement (0, 250, 750, or 1500 mg) was administered in conjunction with a controlled, low Ca diet. • Statistically significant increase in serum levels of P and PTH, and urinary P excretion in relation to increasing P doses. Load of P intake was inversely associated with serum concentrations of biomarkers of bone metabolism.
Karp and others (2007)	16 women Age 20 to 30 y	Total dietary intake (including one P supplement arm)	Randomized, crossover study	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized phosphate-rich diet was consumed. Used different whole food P sources for each arm, with one phosphate supplement arm composed of common phosphate additives. • The effects of high P intake appeared to depend on the source of P consumed. Compared with the control, serum P was increased by all sources, and PTH only increased by P supplement (decreased by cheese, unchanged by meat and whole grains). Based on serum P and urinary P excretion, P from meat and supplements appeared to be absorbed better than P from whole grains.

(*Continued*)

Table A7—Continued.

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Kemi and others (2008)	12 women Age 21 to 40 y	Total dietary intake	Randomized, crossover study	• Markers of Ca and bone metabolism were monitored for 24 h after a randomized Ca supplement dose (0, 600, or 1200 mg) was administered in conjunction with a controlled, high-phosphate diet. • With increasing doses of Ca, serum PTH concentration decreased, serum ionized Ca concentration increased, and BALP did not change. The authors noted that the dietary Ca:P ratio was important and that high Ca intake may not be sufficient to overcome adverse effects of high dietary P intake on Ca metabolism.
Kemi and others (2009)	147 women Age 31 to 43 y	Total dietary intake	Cross-sectional study	• Study of associations between markers of Ca metabolism and habitual dietary P intake, subcategorized by amount of natural and additive P consumed. (Food-additive phosphate considered as processed cheese only.) • Higher total habitual dietary P intake was associated with higher serum PTH levels and lower ionized Ca concentrations; mean serum PTH was almost 2 times higher and the mean serum ionized Ca was lower among participants whose habitual total P intake was the highest compared with those whose intake was the lowest.
Yin and others (2010)	216 boys and girls Age 16 y	Total dietary intake (maternal)	Prospective cohort study	• Assessment of maternal dietary intake during last 3 mo of pregnancy and effects on BMD and BMC of these offspring at an age of 16 y. • Higher P density in the maternal diet was associated with higher BMD in the 8-y-old offspring (although not in the 16-y-old offspring).
Kemi and others (2010)	147 women Age 31 to 43 y	Total dietary intake	Cross-sectional study	• Markers of Ca metabolism were analyzed, and associations made with habitual dietary Ca:P intake ratio. • Results suggest that habitual diets with low Ca:P molar ratios may interfere with homoeostasis of Ca metabolism and increase bone resorption, as indicated by higher serum PTH and urinary Ca concentrations.
Ito and others (2011)	441 women Age 18 to 22 y	Total dietary intake	Cross-sectional study	• A study if the associations between habitual dietary P and Ca intake, and BMD in young Japanese women. • Authors determined that Ca intake and Ca:P ratio had significant positive associations with BMD in the distal radius, but not in the lumbar spine or femoral neck.
Bansal and others (2013)	2767 women Age 45 to 84 y	Not evaluated	Cross-sectional study (from Multi-Ethnic Study of Atherosclerosis)	• Assessment of the association between estrogen therapy and serum Ca and P, FGF-23, urinary excretion of Ca and P, 24,25 dihydroxyvitamin D, and PTH. • Assessment of the association between estrogen therapy and BMD. • Estrogen replacement therapy had a significant association with markers of Ca and P metabolism, including lower mean serum Ca and P levels.
Karp and others (2013)	14 women Age 19 to 31 y	Supplement	Randomized, crossover study	• Markers of Ca metabolism and renal function were monitored for 24 h after a randomized phosphate supplement plus low Ca diet was consumed. • During both phosphate salt sessions, there was an increase in serum P, urinary P, and serum PTH compared with placebo. Results from this study suggest that polyphosphate salts binds to calcium more effectively than monophosphate salts in the small intestine.
Lee and others (2014)	4935 men and women Age 30.5 to 62.9 y	Total dietary Intake	Cross-sectional study	• A Korean study to assess the association and correlation between Ca intake, P intake, and Ca:P ratio with BMD. • After adjusting for covariates, dietary Ca intake and Ca:P ratio were positively related to BMD in the femoral neck of men older than 50 y of age and in premenopausal women. Findings suggest that increased Ca intake and high Ca:P intake ratio might have beneficial effects on bone mass in the Korean population.
Trautvetter and others (2016)	62 men and women Age 18 to 60 y	Supplement	Randomized, controlled study	• Association between markers of mineral and bone metabolism with various levels of Ca intake in the background of a high-phosphate diet. • The authors conclude that a high phosphate intake, without adequate Ca intake, has a negative impact on Ca metabolism and that an adequate calcium-to-P intake ratio is important for normal Ca metabolism.

$1,25(OH)_2D$, 1,25 dihydroxyvitamin D; BALP, bone-specific alkaline phosphatase; BMC, bone mineral concentration; BMD, bone mineral density; Ca, calcium; Ca:P, calcium-to-phosphorus ratio; K, potassium; Mg, magnesium; P, phosphorus; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; Vit D, vitamin D.

Table A8–Studies investigating associations between dietary phosphorus intake or serum phosphorus concentration and cancer risk

Study reference	Study population	Source of phosphorus	Study design	Study description and results
Wilson and others (2015)	47885 men Age 40 to 75 y	Total dietary intake (including supplements)	Prospective cohort	• Evaluation of associations between P and Ca intake and prostate cancer risk, particularly lethal and high grade disease, using a cohort from the Health Professionals Follow-Up Study. • After adjustment for Ca intake, RR increased for all prostate cancers for highest compared with lowest quintile of dietary P intake; RR for high-grade prostate cancer also increased, no association reported for other prostate cancer subtypes.
Kesse and others (2006)	2776 men Age 45 to 60 y	Total dietary intake	Prospective cohort (drawn from placebo-controlled randomized trial)	• Evaluation of associations between dairy product, Ca and P intake and prostate cancer risk in French men participating in the SU.VI.MAX study. • Main finding was a relationship between calcium intake and the risk of prostate cancer, which might be modulated by phosphorus intake.
Tavani and others (2005)	1294 men 1451 controls (46 to 74 y)	Selected foods intake (focus on dairy, and foods rich in Ca, P, or Vit D)	Case-control	• Evaluation of associations between dairy product, Ca, P, and Vit D intake, and prostate cancer risk in Italian men. • At levels consumed in the study population, there was no evidence for an association between dietary P intake and the risk of prostate cancer.
Chan and others (2000)	27062 men Age 50 to 69 y	Total dietary intake	Prospective cohort (drawn from 2 × 2 factorial, placebo-controlled randomized trial)	• Evaluation of associations between Ca and P intake and Stage 2 to 4 prostate cancer risk in male Finnish smokers participating in the ATBC study. • No association for P and total prostate cancer risk in the standard multivariate model used.
Chan and others (1998)	526 men (mean age 70.7 y) 536 controls (mean age 70.6 y)	Total dietary intake (specific dairy, meat, grain, fruit, and vegetable foods)	Case–control	• Evaluation of associations between dairy product, Ca, P, and Vit D intake, and prostate cancer risk in Swedish men. • Dairy and Ca intake was associated with prostate cancer risk. P, while possibly protective, was not risk factor in this population.
Tseng and others (2005)	3612 men Age 25 to 74 y	Total dietary intake	Prospective cohort	• Evaluation of associations between dairy product, Ca, P, and Vit D intake, and prostate cancer risk in NHEFS study participants. • Strong association identified between dairy food intake and prostate cancer risk, and between dietary Ca intake and prostate cancer risk. No association was identified between dietary P intake and prostate cancer risk when Ca was also considered.
Michaud and others (2000)	47909 men Age 40 to 75 y	Total dietary intake (including supplements)	Prospective cohort	• Evaluation of associations between supplement, macro-, and micronutrient intake and bladder cancer risk in men enrolled in the Health Professionals Follow-Up Study. • No association between macronutrient intake and bladder cancer.
Merritt and others (2015)	EPIC: 301107 women, age 25 to 70 y NHS/NHSII: 155406 women, age 25 to 55 y	Total dietary intake	Prospective cohort studies	• Evaluation of associations between food intakes and endometrial cancer risk in the EPIC study, with validation in the NHS/NHSII studies. • Although 1 of the 10 foods and nutrients was associated with endometrial cancer in EPIC, association between P and endometrial cancer was not confirmed among participants in NHS and NHSII: studies.
Boutron and others (1996)	1269 males and females Age 30 to 75 y 2 parts: 362 adenoma cases, 427 polyp-free controls171 cancer cases, 309 controls	Total dietary intake	Case–control	• Assessment of risk of adenoma in subjects who had recently had endoscopy, and assessment of colon cancer risk in population resident in a region of France. • Association not reported between high dietary P or low Ca:P ratio and risk of adenomas. Authors report a trend toward an increased risk of colorectal cancer associated with phosphorus intake in women but not in men.
Kesse and others (2005)	73034 women Age 40 to 65 y 2 parts: 4804 polyp free controls 172 colorectal cancer compared with 67312 controls	Total dietary intake	Prospective cohort	• Evaluation of associations between dairy products, Ca, phosphorus, and Vit D and the risk of adenoma and colorectal cancer in women participating in the French E3N-EPIC study. (Cases and cancer-free cases for adenoma group were selected from a group of participants who had a colonoscopy during the prospective cohort study.) • Significant association between increasing dietary P intake and decreasing RR of adenoma. Similar (not significant) trend for high-risk adenoma and colorectal cancer. • Intakes of P and C had protective effects that might be partially confounded by each other.
Wulaningsih and others (2013)	397292 males and females Age >20 y	Not assessed	Prospective cohort	• Evaluation of associations between serum Pi, total cancer risk, and individual cancer risk using data from the Swedish AMORIS database. • Positive association between serum P quartiles and the risks of cancer of the pancreas, lung, thyroid gland and bone in men, and cancer of the esophagus, lung, and nonmelanoma skin cancer in women. Risks for developing breast and endometrial cancer, as well as other endocrine cancer in both men and women, were lower in those with higher serum P levels.

AMORIS, Apolipoprotein Mortality Risk Study; Ca, calcium; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention; EPIC, European Prospective Investigation into Cancer and Nutrition; E3N-EPIC, Etude Epidemiologique de femmes de la Mutuelle Generale de l'Education Nationale (the French part of the EPIC study); NHEFS, National Health and Nutrition Examination Epidemiologic Follow-up Study; NHS/NHSII, Nurse's Health Studies; P, phosphorus; Pi, inorganic phosphorus; PMID, PubMed identification number; RR, relative risk; SU.VI.MAX, Supplementation en Vitamines et Mineraux Antioxydants; Vit D, vitamin D.
Significant refers to statistically significant.

fracture risk in children and adolescents (Wyshak 2000; Ma and Jones 2004); reduced BMD in women (but not men) who habitually consumed caffeinated colas (Tucker and others 2006); and an acute increase in markers of bone turnover in young men who consumed a low calcium diet in conjunction with large volumes of caffeinated cola (Kristensen and others 2005). The 5th study showed that caffeine, rather than acidulants (citric or phosphoric acid), was responsible for the acute calciuric effect reported in caffeinated colas and other caffeinated beverages (Heaney and Rafferty 2001).

Associations between higher calcium-to-phosphorus intake ratio and favorable measure of markers of bone health or calcium metabolism were reported in all 7 articles addressing this topic (Brot and others 1999; Kristensen and others 2005; Kemi and others 2008; Kemi and others 2010; Ito and others 2011; Lee and others 2014; Trautvetter and others 2016). These associations are indirectly supported by the interventional studies conducted in young women examining the effects of high phosphorus intake in conjunction with a low calcium diet on markers of bone and calcium metabolism (discussed further in Appendix A1.1.2). A reduction in dietary phosphorus absorption by increases in dietary calcium may play a role in these associations (Heaney 2000; Heaney and Nordin 2002). Low calcium intakes and lower calcium-to-phosphorus intake ratios were also in cola drinkers and could have contributed to the lower BMD noted in female cola consumers (Tucker and others 2006).

In one study, phosphorus source was found to play a role in the associations between high phosphorus intake and markers of bone and calcium metabolism; the authors concluded that phosphorus from meat and supplements were better absorbed than phosphorus from whole grains, and only the phosphorus supplement increased PTH levels, whereas all sources increased serum phosphorus levels (Karp and others 2007). Statistically significant increases in PTH levels were reported in the highest (compared with the lowest) quartile of habitual phosphorus consumers as well as in consumers of processed cheese (considered a source of additive phosphate) compared with nonconsumers (Kemi and others 2009). In another study, an association was not detected between dietary phosphorus or calcium intake and BMD in Mexican women who obtained most of their phosphorus and calcium from vegetable sources (Méndez and others 2002).

In one study of children, longitudinal phosphorus intake (between the ages of 2 and 8 y) was directly associated with BMD and BMC at age 8 (Bounds and others 2005); in another study, higher phosphorus density in the maternal diet was associated with higher BMD in the 8-y-old offspring (although not in the 16-y-old offspring) (Jones and others 2000; Yin and others 2010).

Phosphorus intake in pregnancy is further discussed in Appendix A1.2.5; a summary of articles related specifically to bone health in young and premenopausal women is provided in Appendix A1.1.2; and in perimenopausal and postmenopausal women in Appendix A1.1.3.

In elderly men, low phosphorus intake was associated with fracture risk (Elmståhl and others 1998), and, in another study, an association was not detected between cola consumption and BMD in men (in contrast to the findings in women) (Tucker and others 2006).

Overall, although associations were reported in many studies between dietary phosphorus intake and bone health, the associations appear to be complex, to be modified by conutrient intake and the particular food sources of phosphorus, and to differ by the age and sex of the populations studied. Limitations in the usefulness of the evidence provided by this diverse group of studies are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

A1.2.4 Cancer. A total of 11 primary research publications examined the risk of developing cancer. All studies were conducted in adults; 10 examined associations between dietary phosphorus intake and cancer, and one (reported by Wulaningsih and others 2013) examined associations between serum phosphorus intake and cancer. One study examined overall cancer risk as well as the risk of specific cancers in both men and women (Wulaningsih and others 2013); 6 studies examined prostate cancer (Chan and others 1998; Chan and others 2000; Tavani and others 2005; Tseng and others 2005; Kesse and others 2006; Wilson and others 2015); one study examined bladder cancer in men (Michaud and others 2000); one study examined endometrial cancer (Merritt and others 2015); and 2 studies examined colorectal cancer, one in women (Kesse and others 2005) and one in both men and women (Boutron and others 1996).

The report by Wulaningsih and others (2013) is described in Section "Serum phosphorus concentration and clinical outcomes" of the white paper; all the other reports are described in Section "Cancer risk", the evidence they present is summarized in Section "Bone health", and limitations of the studies in contributing to the assessment of the risks or safety of various levels of dietary phosphorus intake are discussed in Section "Summary of evidence: Total dietary phosphorus and clinical outcomes".

In summary, of the 10 studies that examined possible associations between dietary phosphorus intake and cancer risk, 3 studies detected associations and 7 studies did not; of the former, 2 studies reported that higher dietary phosphorus intake was associated with a higher risk of cancer and one study determined the at there was no association. All studies were observational, interpretation of the associations examined is complex; some findings across studies are apparently inconsistent; and, even for single cancer type, there appear to be no general conclusions that can be drawn that extend beyond the studies themselves. The study reported by Wulaningsih and others (2013) indicated that higher serum phosphorus concentrations were associated with a greater overall cancer risk in men but with a lower risk in women.

Characteristics of these publications are presented in Table A8.

A1.2.5 Pregnancy. Two publications reported studies in pregnant women. Both studies evaluated pregnant women enrolled in a birth cohort and started to monitor infants at high risk of sudden infant death syndrome in Tasmania, Australia. The studies examined associations between the diets of women in the last 3 mo of pregnancy and BMD in cohort children some years later. The 1st study (Jones and others 2000) evaluated 173 children at an age of 8 y, while the 2nd study (Yin and others 2010) focused on 216 children at an age of 16 y. At 8 y, higher phosphorus density in the maternal diet during pregnancy was reported to be associated with higher BMD in the children, but a combined statistical model including multiple dietary variables had a better "goodness of fit" than any individual nutrient: children whose mothers were in the ideal dietary exposure categories for potassium, magnesium, phosphorus, protein, and fat had a 5% to 12% higher BMD than those whose mothers were not. In the 2nd study with the 16-y-old children cohort, no statistically significant association was reported between maternal phosphorus intake during pregnancy and BMD in the children. Although the samples of subjects examined at the 2 time points overlapped considerably, the subjects were not exactly the same, and therefore the

analyses taken together did not constitute a truly longitudinal study. Limitations of these 2 studies include those inherent in studies of observational design and the limited reliability of the methods used for quantification of dietary phosphorus intake. These and other relevant methodological limitations are discussed in Section "Methodological difficulties in associating dietary phosphorus with outcomes: Limitations of reviewed studies".

These studies are described in more detail in Section "Total dietary phosphorus, target organs, and biomarkers" of the white paper.

Appendix B

B1 Literature search strategy and publication selection methodology

B1.1 Initial identification of primary research publications. The agreement between the International Food Additives Council (IFAC) and Cato Research (CATO), the company contracted by IFAC to author this white paper, stipulated that, at most, 300 primary publication abstracts were to be reviewed in this white paper: the term "primary publications" was used to designate publications reporting (and not merely discussing) original clinical research conducted in humans. Of these 300 publications, 50 to 100 were to be selected for inclusion in a master table and reviewed in detail for the generation of the white paper.

The PubMed search engine of the U.S. National Library of Medicine was used to identify publications. CATO proposed several search strings for consideration by IFAC and collaborated with IFAC to refine them and select appropriate strings. Considerations that guided selection and refinement of search strings included IFAC's primary goal, namely, to analyze the effect of phosphate additives on the overall health of humans aged ≥3 y, with a focus on evidence supporting or refuting claims that dietary phosphates may cause or contribute to negative health impacts in the general population, in selected age groups, and in subpopulations with, or at increased risk of, certain disease. Publications in languages other than English and publications presenting primarily animal data were excluded by the search string finally selected (String 1, Table B1): such publications were to be included only if they were cited in articles identified by String 1 (or other searches) and considered to be critical to the production of the white paper. In addition, String 1 was modified to produce String 2, which targets publications focusing on persons with prespecified diseases or conditions, or at increased risk of these diseases or conditions, and both String 1 and String 2 were used. All search strings were designed to identify only articles published on or after January 1, 1995.

Searches conducted with String 1 and String 2 were supplemented by searches using other strings: this was done to widen the scope of the search; to provide an indication of the comprehensiveness of the results produced by each string; and to provide reassurance that central publications were unlikely to be missed when the results of the various searches were aggregated. String 3 and String 4 were among the strings used for this purpose.

Several further strategies were used to gain assurance that the searches were adequately wide-ranging and to identify further publications. These strategies included searching for pertinent review articles (String 6) and aggregating citations from those reviews for which bibliographies could be accessed through PubMed. Central citations in publications of authoritative bodies (for example, the European Food Safety Agency (2015) were also included: an example is formulated as a search string (String 5) in Table B1.

After a preliminary review of search results, IFAC and CATO determined that the search strings should be refined to exclude publications focusing on the use of phosphate binders and renal dialysis in the control of dietary phosphorus absorption. The modification implemented is recorded in Table B1, together with the numbers of publications identified by each string before and after modification. Final searches were conducted using the refined strings in November 2015.

B1.2 Publication selection methodology. An aggregated listing was prepared of all publications identified and duplicate entries were eliminated. CATO reviewers then assessed each publication for relevance based on the publication title and abstract. Reviewers considered the central topics to be discussed in the white paper and used their judgment in applying specified criteria. Each publication was to report the results from a human research study (prospective, retrospective, or case studies) and contain the following information:

- An identifiable number of subjects or human specimens
- Criteria used to enroll subjects or populations into, or include specimens in, the study
- Specific methodology, including methodology for making assessments relevant to one or more links in the conceptual chains of causation or association [2] specified for this purpose
- Results including direct or indirect substantiation or refutation of risk

  – Direct substantiation or refutation was to include evidence bearing directly on the causation/association chain linkage, dietary food-additive phosphate content ↔ clinical outcomes.
  – Indirect substantiation or refutation was to include evidence bearing on any other linkage in the causation/association chain, for example dietary food-additive phosphate content ↔ hormonal and other (patho)physiological changes; or change in serum phosphorus concentration ↔ clinical outcomes.

The article was to describe an identifiable safety issue, harm, toxicity, or benefit. The substantiated or refuted risk could be a harm or toxicity in humans in general or in subpopulations of humans. Subpopulations could be those with renal dysfunction or other specific disease states; those with acute medical conditions, such as treatment of diabetic ketoacidosis or treatment of malnutrition in acute alcoholic states; teenagers; or others.

Publications primarily reporting on the following were to be excluded:

- The use of phosphate binders or dialysis to control serum phosphate in patients with chronic renal failure

[2]The following is an example of such a chain of causation or association, used to assist in assessing the relevance of, and in classifying, publications reviewed:Food-additive phosphate content in diet ↔ total phosphorus content in diet ↔ load of ingested phosphorus ↔ phosphorus balance (absorption/excretion) ↔ change in serum phosphorus concentration ↔ hormonal and other (patho)physiological changes ↔ changes in target organs and biomarkers ↔ clinical outcomesSubchains could be composed of nonadjacent links without necessarily including all or any intervening links: e.g., both **food-additive phosphate content in diet ↔ change in serum phosphorus concentration ↔ hormonal and other (patho)physiological changes ↔ changes in target organs and biomarkers** and **change in serum phosphorus concentration ↔ changes in target organs and biomarkers** were considered valid subchains. Search strings were not designed to specifically target any subchains.

Table B1–Search strings and counts of publications identified

String Number	Count[a] Text	BM	AM
1	"Phosphorus, Dietary"[majr] OR (("Phosphates"[majr] OR "Phosphorus"[majr] OR "Hyperphosphatemia"[majr] OR "inorganic phosphate"[ti] OR "inorganic phosphates"[ti] OR "inorganic phosphorus"[ti] OR "phosphoric acid"[tiab] OR diphosphate[tiab] OR polyphosphate[tiab] OR "serum phosphate"[tiab] OR hydroxyapatite[tiab]) AND ("Food Additives"[mh] OR additives[tiab] OR "Dietary Supplements"[mh] OR supplementation[tiab] OR supplements[tiab] OR "Food"[mh] OR "Diet"[mh] OR diet[tiab] OR dietary[tiab] OR nutrition[all fields] OR nutritional[all fields] OR "Recommended Dietary Allowances"[mh] OR ("Dietary reference intake" [tiab] OR "Tolerable upper intake level" [tiab]) OR intake[tiab] OR intakes[tiab] OR consumption[tiab] OR nutrient [tiab] OR nutrients[tiab] OR nutritional[tiab])) **AND** ("Morbidity"[mh] OR "Mortality"[mh] OR "mortality"[sh] OR "adverse effects"[sh] OR "Life Expectancy"[mh] OR "Risk"[mh] OR "Risk Factors"[mh] OR "Safety"[mh] OR outcomes[All Fields] OR "Survival"[mh] OR "Health"[mh] OR "Health Status"[mh] OR harm[tiab] OR harmful[tiab] OR deleterious[tiab] OR deficient[tiab] OR deficiency[tiab] OR injury[tiab] OR injuries[tiab]) **AND** (Case Reports[ptyp] OR Clinical Trial[ptyp] OR Consensus Development Conference[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp] OR Guideline[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp]) **AND** (English[lang]) **AND** ("1995/01/01"[PDAT]: "2015/12/31"[PDAT] **AND "Humans"[mh]**)	256	190
2	"Phosphorus, Dietary"[majr] OR (("Phosphates"[majr] OR "Phosphorus"[majr] OR "Hyperphosphatemia"[majr] OR "inorganic phosphate"[ti] OR "inorganic phosphates"[ti] OR "inorganic phosphorus"[ti] OR "phosphoric acid"[tiab] OR diphosphate[tiab] OR polyphosphate[tiab] OR "serum phosphate"[tiab] OR hydroxyapatite[tiab]) AND ("Food Additives"[mh] OR additives[tiab] OR "Dietary Supplements"[mh] OR supplementation[tiab] OR supplements[tiab] OR "Food"[mh] OR "Diet"[mh] OR diet[tiab] OR dietary[tiab] OR nutrition[all fields] OR nutritional[all fields] OR "Recommended Dietary Allowances"[mh] OR ("Dietary reference intake" [tiab] OR "Tolerable upper intake level" [tiab]) OR intake[tiab] OR intakes[tiab] OR consumption[tiab] OR nutrient [tiab] OR nutrients[tiab] OR nutritional[tiab])) **AND** ("Kidney Diseases"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Vascular Calcification"[Mesh] OR "Neoplasms"[Mesh] OR "Mortality"[Mesh]) **AND** (Case Reports[ptyp] OR Clinical Trial[ptyp] OR Consensus Development Conference[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp] OR Guideline[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp]) **AND** (English[lang]) **AND** ("1995/01/01"[PDAT]: "2015/12/31"[PDAT] **AND "Humans"[mh]**)	170	89
3	(Phosphorus[ti] OR Phosphate[ti] OR phosphates[ti]) AND ("Additives"[ti] OR "Additive"[ti] OR "Recommended Dietary Allowance"[ti] OR "Recommended Dietary Allowances"[ti] OR "Tolerable upper intake level" [tiab] OR intake[ti] OR intakes[ti]) AND (English[lang]) AND ("1995/01/01"[PDAT]: "2015/12/31"[PDAT] AND "Humans"[mh])	95	76
4	(Phosphorus[ti] OR Phosphate[ti] OR phosphates[ti]) AND ("Additives"[tiab] OR "Additive"[tiab] OR "Recommended Dietary Allowance"[tiab] OR "Recommended Dietary Allowances"[tiab] OR "Tolerable upper intake level" [tiab] OR intake[tiab] OR intakes[tiab]) AND (English[lang]) AND ("1995/01/01"[PDAT]: "2015/12/31"[PDAT] AND "Humans"[mh]) **AND** (Case Reports[ptyp] OR Clinical Trial[ptyp] OR Consensus Development Conference[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp] OR Guideline[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR "Cohort studies"[MeSH])	131	103
5	20083730[UID] OR 16735491[UID] OR 15883550[UID] OR 16869716[UID] OR 11075876[UID] OR 20675668[UID] OR 17502528[UID] OR 19754972[UID] OR 11305263[UID] OR 11083482[UID] OR 16512941[UID] OR 15880532[UID] OR 19948843[UID] OR 11130620[UID] OR 21292817[UID] OR 21054294[UID] OR 21570529[UID] OR 15905998[UID] OR 15883441[UID] OR 19965546[UID] OR 19756026[UID]	NA	NA
6	"Phosphorus, Dietary"[majr] AND review [ptyp]	64	48

AM, after modification; BM, before modification; NA, not applicable.
[a] Each search was conducted before and after the following clause was appended to the search string being used: NOT ("binder"[tiab] OR "hemodialysis" [tiab] OR "haemodialysis" [tiab] OR "dialysis" [tiab]).

- Dietary supplementation of a nutrient other than phosphorus (but in a compound containing phosphorus, for example, iron phosphate) to assess the therapeutic or preventative potential of the intervention

Publications reporting on supplementation of phosphorus with the experimental, nontherapeutic intention to increase intake and so simulate the effects of a (habitual) diet that is higher in phosphorus content were not to be excluded. Such supplementation was not regarded as "dietary supplementation," which has a therapeutic potential and intent.

The abstract of each publication was reviewed according to these criteria by 2 CATO reviewers and discrepant determinations were resolved. The list of publications was provided to IFAC, together with CATO's determinations. IFAC was to identify possible omissions from the list and indicate their agreement on the publications to be excluded. If review of the full text of a publication revealed that it did not satisfy the inclusion criteria, even though it appeared to do so, on the basis of the review of its abstract, the article was removed from the inclusion list. The finalized list was used to prepare the master clinical table.

B1.3 Supplementary search and selection activities. Throughout the production of the white paper, CATO performed additional *ad hoc* searches and applied the selection criteria to the identified articles. Further relevant publications were identified from citations included in the articles already selected for inclusion.

The scope of the white paper is very broad, and investigation in the field has been very active over many years. However, progressively fewer publications were identified during these supplementary activities, and almost all data in the additional publications merely confirmed conclusions that could be drawn from data in publications already included. Although it is impossible to know if every primary publication relevant to the subject matter of the white paper has been identified and considered for inclusion, CATO considers that the current literature on relevant topics is well represented in the white paper.

Appendix C

C1 Evaluation of the quality of evidence

Each published clinical study that was identified in the literature search and included in the white paper was reviewed to determine the strength of the evidence presented in evaluating associations of dietary phosphorus, phosphorus concentrations in body fluids, and excreted phosphorus with different variables. The design of each study was considered as the principal characteristic in determining the quality of evidence. The quality rating for each study was broadly informed by the FDA guidance "Evidence-Based Review Systems for the Scientific Evaluation of Health Claims" (FDA 2009). Studies were assigned quality ratings according to the following criteria:

- High level: randomized (blinded or unblinded), controlled clinical trial
- Moderate level: prospective, interventional, or noninterventional cohort studies
- Low level: observational, noninterventional study including case–control, retrospective, and cross-sectional or sample-survey designs

Appendix D

D1 Master clinical table

Table D1 contains a categorized list of the primary research publications reviewed in the white paper "Dietary Food-Additive Phosphate and Human Health." Each publication is listed together with summary information describing the study it reports and is assigned to a category according to the focus of the study.

Some studies focused directly on possible relationships between dietary food-additive phosphorus intake and morbidity or mortality; most, however, examined only one or more intermediate linkages in putative chains of (causal or noncausal) associations such as the following:

Food-additive phosphate content in diet ↔ total phosphorus content in diet ↔ load of ingested phosphorus ↔ phosphorus balance (absorption/excretion) ↔ change in serum phosphorus concentration ↔ hormonal and other (patho)physiological changes ↔ changes in target organs and biomarkers ↔ clinical outcomes (health, morbidity, mortality).

The executive summary of the white paper lists an array of methodological limitations revealed by analysis of the studies. Some of these limitations were common to many of the studies; every study was affected by at least one of the limitations. The limitations weakened the reliability of the findings of the studies, decreased the strength of the evidence they could

Table D1–Master clinical table: dietary food-additive phosphate and human health

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
FOOD-ADDITIVE PHOSPHATE CONTENT IN DIET: Associated with change in serum phosphorus concentration					
Moore and others (2015) 26040641	Association of dietary phosphate and serum phosphorus concentration by levels of kidney function	• Cross-sectional study of adults with reduced kidney function. • 7895 adults (age: 20 to 85 y).	Dairy products and cereals/grains with inorganic phosphate additives	• Dairy products (with or without inorganic phosphate additives), cereals and grains (with inorganic phosphate additives) significantly increased serum P levels.	Low
Gutiérrez and others (2012) 22217539	Associations of socioeconomic status and processed food intake with serum phosphorus concentration in community-living adults: the Multi-Ethnic Study of Atherosclerosis (MESA)	• Cross-sectional study. • 2664 adults with no clinically evident CVD. • Measured fasting serum phosphate levels.	Processed foods enriched with P-based food additives	• Lower income and lower educational achievement categories were associated with modestly higher serum P. • Each serving per day higher soda intake was associated with 0.02 mg/dL lower serum phosphorus. • Greater intake of foods commonly enriched with P additives was not associated with higher serum P.	Low
Gutiérrez and others (2010) 20847142	Low socioeconomic status associates with higher serum phosphate irrespective of race	• Cross-sectional study of the Chronic Renal Insufficiency Cohort Study. • 2879 patients with CKD. • Assessed diet, blood samples, and socioeconomic status.	Processed and fast foods enriched with highly absorbable P additives	• Greater serum phosphate levels in black than white subjects. • Subjects with lowest incomes or unemployed had higher serum phosphate levels than subjects with the highest incomes or who were employed. • Both blacks and whites with the lowest incomes had higher phosphate levels than whites with highest incomes.	Low
TOTAL PHOSPHORUS CONTENT IN DIET: Associated with change in serum phosphorus concentration					
Mataix and others (2006) 16967192	Factors influencing the intake and plasma levels of calcium, phosphorus and magnesium in southern Spain	• Cross-sectional study. • 3421 subjects: 1747 men, 1674 women (age: 25 to 60 y). • Food consumption was assessed by a 48-h recall. • Blood samples were obtained for biochemical analysis in a random subsample of 354 subjects.	Dietary P	• Sex, age, educational level, obesity, smoking, alcohol use, and physical activity were associated with differences in nutrient intakes. • Analysis of blood samples indicated no significant correlations between the intakes and plasma levels of P, Ca, and Mg. • Obese people (body mass index: ≥ 30 kg/m^2) consumed less Ca, P, and Mg. • Low plasma Ca concentrations were associated with female sex and older age. • Plasma concentrations of Ca only were significantly lower ($P < 0.05$) in obese people than in nonobese people.	Low
CHANGE IN SERUM PHOSPHORUS CONCENTRATION: Associated with target organ effects or biomarkers					
Haraikawa and others (2012) 23419404	A study of the association between serum bone-specific alkaline phosphatase and serum phosphorus concentration or dietary phosphorus intake	• Observational study. • 193 Japanese adults, 97 males and 96 females (mean age: 22.1 $\pm$ 1.8 y). • Dietary nutrient intakes were measured based on 3-d food records. • Serum biochemical markers were measured from fasting blood samples.	Dietary P	• There was a significant negative correlation between dietary P intake and serum BALP activity ($r = -0.226$; $P = 0.002$). • Serum BAP activity was significantly correlated with serum P concentrations ($P = 0.022$). • Serum P concentration was significantly correlated with dietary P intake ($P = 0.011$). • Serum BAP was negatively correlated with Ca intake ($P = 0.01$) and positively correlated with serum FGF-23 ($P = 0.008$) and with serum ALP ($P < 0.001$).	Haraikawa and others (2012) 23419404

(*Continued*)

Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Saab and others (2010) 20580478	Association of serum phosphorus with left ventricular mass in men and women with stable cardiovascular disease: data from the Heart and Soul Study	• Cross-section of an observational study. • 978 outpatients with stable CVD, 181 female, 797 male (mean age: 67 y). • Fasting serum P levels at each visit. • Transthoracic echocardiography was used to measure LVM.	Dietary information not provided	• Women had statistically significantly higher serum P levels than men. • Higher serum P levels were associated with greater LVM in men, but not in women. • In men, each 1-mg/dL higher serum P level was associated with 4.52-g/m^2 greater LVM.	Low
Tuttle and Short (2009) 19965546	Longitudinal relationships among coronary artery calcification, serum phosphorus, and kidney function	• Long-term observational study • 883 adults (age: ≥18 y). • Assessed every 2 y for ≥6 y CAC and CVD risk factors.	Dietary P	• After 6 y, new onset CAC developed in 33% (of subjects yielding an overall prevalence of 50%). • Higher serum P concentration (and reduced kidney function) was an independent predictor of new onset or worsening CAC. • Each 1-mg/dL increase in P-imparted ORs for CAC of 1.61 (incidence) and 1.54 (prevalence).	Low
CHANGE IN SERUM PHOSPHORUS CONCENTRATION: Associated with physiological outcomes					
Bansal and others (2013) 24092825	Influence of estrogen therapy on calcium, phosphorus, and other regulatory hormones in postmenopausal women: the MESA study	• Observational study. • 2767 postmenopausal women (mean age: 64 y). • BMD was measured by abdominal computed tomography.	Estrogen therapy: no mention of P intake	• Mean serum P was lower ($P < 0.001$] and fraction eliminated phosphorus ($P = 0.007$) was higher in women on estrogen therapy. • The adjusted results demonstrated that mean FGF-23 did not differ between women who used or did not use estrogen therapy. • The use of estrogen replacement therapy was significantly associated with higher BMD.	Low
CHANGE IN SERUM PHOSPHORUS CONCENTRATION: Associated with clinical outcomes					
Lorenzo and others (2014) 24763850	Calcium and phosphate concentrations and future development of type 2 diabetes: the Insulin Resistance Atherosclerosis Study	• Epidemiological study. • 863 adults (mean age ranges: 54.4 ± 0.3 to 56.5 ± 0.7 y) with no baseline DM. • Mean 5.2 y follow-up. • Type 2 diabetes was assessed during baseline visit and at follow-up visits.	Dietary P	• CaP product (OR: 1.29; 95% CI: 1.04 to 1.59) were associated with incident diabetes. • Elevated serum Ca and CaP products were associated with increased risk of developing Type 2 diabetes independently of measured glucose, insulin secretion, and insulin resistance.	Low
Hartman and others (2013) 23652556	Can salivary phosphate levels be an early biomarker to monitor the evolvement of obesity?	• Cross-sectional study. • 77 children (mean age: 10.5 ± 1.8y). • Saliva and blood samples were collected under fasting conditions. • Phosphate measured using gas chromatography/mass spectrometry.	Dietary P	• There was a significantly higher salivary phosphate content in obese children than in normal-weight children. There was no association of obesity with plasma phosphate concentrations.	Low
Wulaningsih and others (2013) 23706176	Inorganic phosphate and the risk of cancer in the Swedish AMORIS study	• Observational study of the AMORIS database. • 397292 subjects (age: ≥20 y) • Follow-up of 12.75 y.	Dietary P	• High serum P was associated with cancer in men. • Higher overall cancer risk with increasing serum Pi levels in men (HR: 1.02; 95% CI: 1.00 to 1.04) and a negative association in women (HR: 0.97; 95% CI: 0.96 to 0.99).	Low

(*Continued*)

Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
O'Seaghdha and others (2011) 21292817	Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease	• Cross-sectional study. • 13372 subjects in NHANES III (mean age: 44.3 y) and 2269 subjects from the FHS (mean age: 42 y). • Evaluated relationship between baseline phosphorus levels and risk of CKD or ESRD. • The median follow-up was 25.1 y.	Dietary information not available for subjects	• FHS participants in the highest P category had an increased risk of CKD. • NHANES III subjects with P levels ≥4 mg/dL demonstrated an increased risk of incident ESRD compared with subjects with P levels <4 mg/dL. • Serum P levels in the upper-normal range were associated with a doubling in the risk of developing incident CKD and ESRD.	Low
Taylor and others (2011) 21570529	Plasma fibroblast growth factor 23, parathyroid hormone, phosphorus, and risk of coronary heart disease	• Nested case–control study. • 422 men (mean age: 63.6 ± 8.6 y). • Prospectively examined associations between plasma FGF-23, PTH, and serum phosphorus and risk of CHD in men from the Health Professionals Follow-up Study.	Dietary P	• No statistically significant differences between subjects in plasma levels of FGF-23, PTH, or P. • Plasma FGF-23, PTH, and P were not associated with the development of incident CHD in men without CKD.	Low
Dhingra and others (2010) 20675668	Relations of serum phosphorus levels to echocardiographic left ventricular mass and incidence of heart failure in the community	• Prospective cohort of associations between serum P concentrations and the development of heart failure (included nested cross-sectional study of associations between serum P and LVM). • 3300 adults (mean age: 44 y) from Framingham Offspring Study (3088 included in cross-sectional study). • Fasting blood samples collected (LVM assessed by cardiac echo).	Dietary information not available	• Each mg/dL increment in serum P was associated with a 1.74-fold increase in risk of heart failure. • Individuals in the highest serum P quartile experienced a 2-fold increase in risk of heart failure compared with participants in the lowest quartile. • In analyses restricted to individuals with normal renal function (eGFR >90 mL/min/1.73 m^2), no proteinuria and serum P levels <4.5 mg/dL, there was a trend of higher incidence of heart failure with greater serum phosphorus ($P = 0.02$) • In this subgroup, the association of serum P with heart failure remained robust.	Low
Heimburger and others (2010) 20502700	Serum phosphate predicts early mortality in adults starting antiretroviral therapy in Lusaka, Zambia: a prospective cohort study	• Observational cohort. • 142 HIV-infected adults (median age: 32 y). • The initial visit included a detailed health and 24-h dietary intake history, review of systems, physical examination, and laboratory testing. • Followed prospectively for 12 wk of ART.	Dietary P (P supplements given to subjects with low serum P)	• Low serum phosphate at ART initiation was an independent predictor of early mortality among HIV patients with severe malnutrition or advanced immunosuppression. • Each 0.1-mmol/L increase in baseline phosphate was associated with an incremental decrease in mortality.	Low
Larrson and others (2010) 19948843	Conjoint effects of serum calcium and phosphate on risk of total, cardiovascular, and noncardiovascular mortality in the community	• Prospective, community-based cohort. • 2176 men (mean age; 50.1 y). • Mean 29.8 y follow-up. • At the age of 50 y, the participants completed a questionnaire about their smoking habits and medical history and underwent a physical examination. • All blood samples were obtained in the morning after an overnight fast.	Dietary P	• Higher serum concentrations of Ca, Pi, and CaxPi were associated with higher total mortality risk in middle-aged men. • Higher serum concentration of Ca was mainly related to non-CV mortality. • Higher serum concentration of Pi and CaxPi were related to CV mortality.	Low

(*Continued*)

Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Ix and others (2009) 19211667	Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA	• Cross-sectional study of the MESA prospective cohort. • 1370 adults with no CVD (mean age: 64 ± 10 y). • Dietary history and blood specimens were provided after an overnight (8-h) fast.	Dietary P	• Higher serum P concentrations were associated with higher levels of LDL, HDL, CRP, and lower eGFR. • P levels >4 mg/dL had approximately twice the prevalence of high vascular stiffness. • There was a strong and independent association of higher serum P concentrations with high arterial stiffness among individuals without clinically recognized CVD.	Low
Foley and others (2009) 18987306	Serum phosphorus levels associate with coronary atherosclerosis in young adults	• Cross-sectional study of the prospective CARDIA cohort. • 3015 healthy young adults (mean age: 25.2 y). • Serum P levels were measured at baseline, and CAC was assessed by computed tomography 15 y later.	Dietary P	• Higher serum P levels were associated with high CAC and may represent a risk factor for coronary artery atherosclerosis in healthy young adults. • Serum Ca and Ca-P product levels had no association with CAC.	Low
Foley and others (2008) 18760141	Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study	• Cross-sectional analysis of the ARIC. • 15732 adults (mean age: 54.2 y). • Subjects were evaluated over a period of 12.6 y.	Dietary P	• Low levels of P were associated with CHD and high levels with death. • Serum P levels were associated with stroke and death but not CHD. • Low levels of CaP product were associated with CHD (HR 0.92), and high levels of CaP product were associated with stroke (HR 1.10) and death (HR 1.13).	Low
Onufrak and others (2009) 18980959	Investigation of gender heterogeneity in the associations of serum phosphorus with incident coronary artery disease and all-cause mortality	• Prospective cohort of the ARIC. • 13998 adults (age: 45 to 64 y). • Blood specimens were provided after 8-h fasting.	Dietary information not available	• Men in the highest quintile of serum P level (>3.8 mg/dL) had increased CAD and mortality rate. • No association of CAD or mortality with serum P in women. • There was no significant association of serum P concentrations with CAD and sex ($P = 0.195$).	Low
Dhingra and others (2007) 17502528	Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community	• Cross-section of the Framingham Offspring Study. • 3368 adults (mean age: 44 y) free of CVD and CKD. • Subjects had a physical examination at each visit.	Dietary P	• Higher level of serum P was associated with an increased in heart failure. • Individuals in the highest serum P quartile experienced a 1.55-fold (95% CI: 1.16 to 2.07) increased risk of CVD compared with individuals in the lowest quartile.	Low
Tonelli and others (2005) 16246962	Relation between serum phosphate level and cardiovascular event rate in people with coronary disease	• *Post hoc* analysis of the Cholesterol and Recurrent Events study (pravastatin compared with placebo). • 4127 adults (mean age range 57 to 59 y). • Baseline phosphate levels were measured in fasting participants. • Followed up for a median of 59.7 mo.	Dietary P	• Higher serum P levels were associated with increased risk of new heart failure, MI, and the composite of coronary death or nonfatal MI, but not the risk of stroke. • Serum P inversely correlated with kidney function when baseline GFR <60 mL/min/1.73 m^2 and directly correlated with kidney function when baseline GFR ≥60 mL/min/1.73 m^2. • Baseline serum phosphate levels were significantly associated with the age-, race-, and sex-adjusted risk of all-cause death (HR per 1 mg/dL = 1.27; 95% CI: 1.02 to 1.58; $P = 0.03$).	Low

(*Continued*)

Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Food-additive PHOSPHATE content in diet: Associated with target organ effects or biomarkers					
Mazariegos-Ramos and others (1995) 7776100	Consumption of soft drinks with phosphoric acid as a risk factor for the development of hypocalcemia in children: a case–control study	• Case–controlled study • 228 children (mean age: 5.6 ± 2.4 y) • 1:3 ratio of children with 57 cases with serum Ca <2.2 mmol/L to 153 controls with serum Ca >2.2 mmol/L • Assessed if consumption of ≥1.5 L/wk of soft drinks with phosphoric acid was associated with increased risk of hypocalcemia	Cola soft drinks containing phosphoric acid	• There was a statistically significant association between consumption of at least 1.5 L/wk of soft drinks containing phosphoric acid and the development of hypocalcemia (OR = 5.27; 95% CI: 3.17 to 8.75; $P < 0.001$).	Low
Itkonen and others (2013) 23841978	Associations among total and food additive phosphorus intake and carotid intima-media thickness–a cross-sectional study in a middle-aged population in Southern Finland	• Cross-sectional study • 546 adults: 176 males and 370 females (mean age: 41.9 ± 2.8 y) • Dietary intake data were collected using a 3-d FFQ • Carotid IMT was measured by ultrasonography, and biomarker measurements were assessed from 12-h fasting blood samples.	Food-additive phosphorus	• No statistically significant associations between TP or FAP intake and IMT. • Female subgroup had a statistically significant difference in IMT between the highest and lowest quintiles of TP intake ($P = 0.035$), with higher TP associated with higher IMT. • Positive trend between energy-adjusted TP intake and IMT among all subjects ($P = 0.039$). • Significant positive linear trend between FAP intake and IMT ($P = 0.022$).	Low
Tucker and others (2006) 17023723	Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study	• Cross-sectional study of Framingham Osteoporosis Study. • 2538 adults, 1413 females (mean age: 58.2 ± 9.4 y) and 1125 males (mean age: 59.4 ± 9.5 y). • Dietary intake data were collected using FFQ. • BMD assessments were performed by DEXA bone density scans.	Cola soft drinks containing caffeine and phosphoric acid	• TP intake was not significantly higher in daily cola consumers than in nonconsumers; however, the Ca:P intake ratios were lower. • Intake of cola, but not of other carbonated soft drinks, was associated with reduced BMD in the hip for women. • No significant associations of caffeinated cola beverage consumption with spine BMD were observed for either men or women.	Low
TOTAL PHOSPHORUS CONTENT IN DIET: Associated with target organ effects or biomarkers					
Lee and others (2014) 25496564	Association between dietary calcium and phosphorus intakes, dietary calcium/phosphorus ratio and bone mass in the Korean population	• Cross-sectional study. • 4935 adults, 2309 men (age: 30.4 to 61.3 y) and 2,626 women (age: 30.5 to 62.9 y). • Used dietary data from the Korean National Health and Nutrition Examination Survey.	Dietary P	• Dietary Ca intake and dietary Ca:P ratio intake were positively related to BMD for femoral neck in men aged >50 y ($P =$ 0.046 and 0.041, respectively). • Dietary Ca and Ca:P intake was related to lumbar spine BMD positively and to whole body BMD negatively in men aged <50 y. • In premenopausal women, dietary Ca intake showed positive associations with whole body BMD. • No association was reported between P intake and BMD in any skeletal region of the subjects.	Low
Kwak and others (2014) 24925973	Dietary intake of calcium and phosphorus and serum concentration in relation to the risk of coronary artery calcification in asymptomatic adults	• Cross-sectional study. • 23652 healthy Korean adults age 40.8 ± 7.3 y. • Dietary intake data were collected using self-administered FFQ. • CAC scoring assessed by cardiac computed tomography. • Blood samples taken after at least 10 h of fasting.	Dietary P	• Dietary Ca and P intake was not consistently associated with CAC scores. • Serum Ca, P, and calcium-phosphorus product levels were significantly associated with the CAC score ratios. • Elevated serum levels of Ca, P, and calcium-phosphorus product, but not dietary consumption, were associated with increased CAC scores.	Low

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Yamamoto and others (2013) 23283134	Dietary phosphorus is associated with a significant increase in left ventricular mass	• Cross-sectional study of the MESA. • 4494 community-based individuals with no CVD (age: 45 to 84 y). • Dietary intake data were collected using FFQ. • LVM was measured using MRI. • Regression models used to determine associations of dietary P with LVM and LVH.	Dietary P	• Each quintile increase in the estimated dietary phosphate intake was associated with an estimated 1.1 g greater LVM. • Higher dietary P intake was associated with greater odds of LVH among women, but not among men. • There were no significant differences in the associations of estimated dietary phosphorus with LVM according to the different types of dietary protein or processed food status. • When adjusted for differences in sex, higher estimated dietary P was associated with greater LVM, and the association was stronger among women (particularly postmenopausal women).	Low
Yin and others (2010) 19756026	The association between maternal diet during pregnancy and bone mass of the children at age 16	• Prospective, observational study. • 216 adolescents (mean age: 16.2 ± 0.4 y). • Dietary intake during the 3rd trimester of pregnancy was measured with a self-administered FFQ completed shortly after birth. • BMD in the adolescents of the femoral neck, lumbar spine and total body by DEXA scan.	Dietary P	• Maternal nutrients (protein, Ca, or P density) intakes were not associated with total body BMD in adolescents (using univariate or multivariate analyses). • Positive association between P, Ca, and Mg density intake during pregnancy and lumbar spine BMD (all $P < 0.05$) of the adolescents. • Milk intake during pregnancy was positively associated ($P < 0.05$) with lumbar spine BMD of the adolescents.	Low
Alonso and others (2010) 20083730	Dietary phosphorus, blood pressure, and incidence of hypertension in the atherosclerosis risk in communities study and the Multi-Ethnic Study of Atherosclerosis	• Cross-sectional study from the ARIC and the MESA. • 13444 subjects (age: 45 to 64 y). • Dietary intake was measured with a 66- or 120-item FFQ. • BP was measured with random-zero sphygmomanometer.	Dietary P	• Higher P intake was significantly associated with lower levels of SBP and DBP in both cohorts. • An increase in P intake was associated with lower risk of hypertension in both men and women. • Only higher P intake from dairy products, but not other dietary sources, was associated with lower levels of SBP and lower risk of hypertension.	Low
Elliott and others (2008) 18250363	Dietary phosphorus and blood pressure: international study of macro- and micronutrients and blood pressure	• Cross-sectional study. • 4680 adults (age: 40 to 59 y). • Association of P intake with BP. • Four 24-h dietary recalls. • Japan, China, the United Kingdom, and the United States.	Total dietary P	• Dietary P was inversely associated with BP. • Changes in BP ranged from −1.13 to −2.31 mm Hg for SBP and from −0.59 to −1.47 mm Hg for DBP per additional 232 mg/1000 kcal of P intake. • Correlations between Ca and P; and Mg and P, which were also inversely associated with BP.	Low
Bounds and others (2005) 15883550	The relationship of dietary and lifestyle factors to bone mineral indexes in children	• Cross-sectional study. • 52 children, 25 male and 27 female. • Nutrient intake (from age 2 mo to 8 y) was collected on 9 occasions from 3 d of dietary information. • BMC and BMD measurements of the children (at age of 6 and 8 y) and their mothers were performed by DEXA scan.	Dietary P	• Nutritional intake (P, energy, Ca, protein, Mg, and zinc) was significantly and positively correlated with total BMC. • Nutritional intake (P, energy, protein, and Mg) was significantly and positively correlated with total BMD. • Longitudinal bone mineral indexes, from age 6 and 8 y showing the changes in bone measures over time were highly significant for total BMC.	Low
Méndez and others (2002) 12464724	Effects of calcium and phosphorus intake and excretion on bone density in postmenopausal women in Hermosillo, Mexico	• Prospective, observational cohort. • 47 postmenopausal women (age: 45 to 63 y). • Dietary intake was assessed twice, by 24-h recall. • BMD measurements of the forearm and heel were assessed by DEXA scan.	Dietary P	• Dietary intake of P and Ca had no relation to bone density. • Age, U-Ca, Ca/creatinine, and years of postmenopause had highest negative correlation.	Low

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Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Jones and others (2000) 11083482	Maternal diet during pregnancy is associated with bone mineral density in children: a longitudinal study	• Observational study. • 173 children (mean age: 8 y). • Bone mass at the lumbar spine and femoral neck were measured by DEXA scans. • Maternal dietary intake during the 3rd trimester was measured using a FFQ and 4 y afterwards 2 similar FFQ's were used for mother and child.	Dietary P	• BMD was positively associated with Mg and P of the maternal diet. • Statistically significant associations were identified between P and fat intakes and lumbar spine BMD. • Only milk intake during pregnancy was significantly associated with femoral neck BMD in the children. • Results show substantial association between in utero diet in a well-nourished population and later bone mass in their children but does not identify dietary components of greatest importance.	Low
Teegarden and others (1998) 9734757	Dietary calcium, protein, and phosphorus are related to bone mineral density and content in young women	• Cross-sectional study. • 215 women (age: 18 to 31 y). • Dietary intake was assessed by a FFQ. • Total body, spine, and femoral neck BMD and BMC were assessed by DEXA scans.	Dietary P	• A complex relation among Ca, protein, or P, and the calcium:protein or Ca:P ratio and spine or total-body BMC and BMD. • A single ratio of calcium:phosphorus or calcium:protein did not optimize bone mass across the range of calcium intakes. • Positive correlation between protein, Ca, and phosphate intakes and BMD of the radius and spine as well as BMC of the spine.	Low
Trachtman and others (1995) 7579065	The relationship between calcium, phosphorus, and sodium intake, race, and blood pressure in children with renal insufficiency: a report of the Growth Failure in Children with Renal Diseases Study	• Retrospective analysis of the Growth Failure in Children with Renal Diseases Clinical Trial. • 118 children (age: 18 mo to 10 y). • Nutritional intake was obtained over a 4-d period by a trained dietitian. • Patient BP was measured with a mercury gravity manometer and by auscultatory methods.	Dietary P	• No differences between white and black children in mean Ca, P, or sodium intake. • Mean SBP and DBP for all subjects were normal; no statistically significant differences between white and black children. • Dietary P intake was directly related to DBP in white children ($P = 0.011$); in black children, it was related to both SBP ($P = 0.011$) and DBP ($P = 0.015$). • Among all subjects, the SBP ($P = 0.022$) and DBP ($P = 0.001$) were significantly related to mean daily P intake, but were unrelated to Ca intake.	Low
FOOD-ADDITIVE PHOSPHATE CONTENT IN DIET: Associated with physiological outcomes					
Kemi and others (2009) 19216809	Habitual high phosphorus intakes and foods with phosphate additives negatively affect serum parathyroid hormone concentration: a cross-sectional study on healthy premenopausal women	• Cross-sectional study. • 147 healthy premenopausal women (age: 31 to 43 y). • Study of whether natural P or food-additive phosphates of habitual diets differ in their effects on markers of Ca and bone metabolism and their impact on markers of Ca metabolism. • 4-d food record, fasting blood samples, 24-h urine samples.	Total dietary P, dairy P (as milk and cheese), and food-additive phosphates (as processed cheese)	• Mean S-PTH concentration was higher ($P = 0.048$) and mean serum ionized Ca was lower ($P = 0.016$) in the highest P intake quartile. • Mean S-PTH concentrations were higher in participants who consumed processed cheese compared with nonconsumers and lower consumers of milk and cheese other than processed cheese (but the results were not statistically significant).	Low
Kristensen and others (2005) 15886860	Short-term effects on bone turnover of replacing milk with cola beverages: a 10-d interventional study in young men	• Controlled, crossover, intervention study. • 11 men (age: 22 to 29 y). • Low-Ca basic diet in two 10-d intervention periods (2.5 L of Coca Cola or semi-skimmed milk) with an intervening 10-d washout. • Dietary P and Ca were calculated using a Danish computerized nutrient database. • Serum and plasma samples obtained from 12-h fasting blood samples.	Coca Cola or semiskimmed milk	• Increases in $1,25(OH)_2D$ ($P = 0.019$), PTH ($P = 0.020$), and osteocalcin ($P = 0.014$) were observed during the cola period compared with the milk period. • There were no changes in serum P levels during the cola period but serum P significantly increased during the milk period. • Intake of cola with a low-calcium diet for 10 d induced increased bone turnover as compared with that after a high intake of milk with a low-Ca diet.	Moderate

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Heaney and Rafferty (2001) 11522558	Carbonated beverages and urinary calcium excretion	• Incomplete random block design. • 30 females (mean age: 31.4 ± 5.6 y). • Habitual consumers of carbonated beverages.	Carbonated beverages (with or without caffeine) with phosphoric or citric acid as acidulant	• There was little urinary Ca excretion with any of the beverages. • Excess urinary Ca associated with consumption of carbonated beverages is confined to caffeinated beverages; acidulant type (phosphoric or citric acid) had no acute effect.	High
TOTAL PHOSPHORUS CONTENT IN DIET: Associated with physiological outcomes					
Muras and others (2013) 24092829	Diabetes modifies effect of high-phosphate diet on fibroblast growth factor-23 in chronic kidney disease	• Prospective, controlled, interventional, short-term study. • 26 subjects with Stages 3 to 5 CKD (15 DM, 11 non-DM). • 7-d normal P diet (700 ± 100 mg/d) followed by 6-d high P diet (1800 mg/d). • Serum and urine samples collected.	Total dietary P, plus phosphate supplement	• FGF-23 secretion impaired after phosphate load in DM patients but not in non-DM patients. • In DM patients (despite FGF-23 secretion impairment), there was no significant increase in serum P concentration and no significant change in urine phosphate excretion. • More pronounced FGF-23 response in non-DM subjects suggests inhibition of PTH secretion by high FGF-23 secretion. • PTH seems to play the major role in the regulation of phosphate excretion in subjects with CKD who have DM.	Moderate
Houston and others (2013) 22406119	Associations of dietary phosphorus intake, urinary phosphate excretion, and fibroblast growth factor 23 with vascular stiffness in chronic kidney disease	• Cross-sectional study. • 74 subjects with Stage 3 or 4 CKD (not yet requiring hemodialysis). • Determination of whether markers of P metabolism are associated with increased arterial stiffness measured as augmentation index (AI) in kidney disease. • 4-d food records and blood and urine samples.	Total dietary P	• No associations of estimated daily P intake, serum P, urinary P excretion, or FGF-23 with AI. • No significant difference in serum phosphate concentration across stages of kidney function. • Urinary phosphate excretion decreased as creatinine clearance decreased. • Plasma FGF-23 levels were directly associated with serum phosphate levels and inversely correlated with creatinine clearance. • No association between FGF-23 and daily P intake or urinary phosphate excretion.	Low
Ito and others (2011) 21859660	The relationship between habitual dietary phosphorus and calcium intake, and bone mineral density in young Japanese women: a cross-sectional study	• Cross-sectional study. • 441 Japanese women (age: 18 to 20 y). • Blood and urine samples collected under fasting conditions. • BMD in the distal one-third of radius forearm, lumbar spine and leg femoral neck was measured by DEXA scan.	Dietary P	• Higher Ca intake and a higher Ca:P intake ratio were each significantly associated with greater BMD in the distal radius, but not with BMD in the lumbar spine and femoral neck.	Low
Delgado-Andrade and others (2011) 20122814	Increased intake of Maillard reaction products reduces phosphorus digestibility in male adolescents	• Randomized, 2-period, crossover trial. • 20 healthy males (age: 11 to 14 y). • 14 d on each diet, with 40-d washout between diets. • P balance assessment on last 3 d of each diet, and fasting blood sample collection on the last day of each diet.	Total dietary P (standardized diet, either rich or poor in Maillard reaction products [MRP])	• Increased daily P fecal excretion (not statistically significant) after rich MRP diet compared with poor MRP diet which led to significant reductions in P apparent absorption and fractional absorption of P. • Serum parameters remained unchanged between diets and within normal values. • Consumption of a rich-MRP diet had a negative influence on dietary P absorption, tending to decrease the P balance.	High

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Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Moe and others (2011) 21183586	Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease	• Randomized, crossover trial. • 9 patients (mean age: 61 ± 8.4 y) with CKD (mean eGFR: 32.3 ± 6 mL/min). • Subjects received each diet for 7 d, in randomized order, separated by a 2- to 4-wk washout. • Blood and urine collected 30 min after each of the 3 meals during last 24 h of each diet.	Total dietary P (equal calories, P, Ca, and sodium from vegetarian compared with meat diet)	• Despite equivalent protein and P concentrations in the diets, subjects had lower plasma P levels, decreased urine 24-h P excretion, and significantly decreased FGF-23 levels on the vegetarian diet compared with the meat-based diet.	High
Gutiérrez and others (2011) 22034506	Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the Health Professionals Follow-up Study	• Cross-sectional cohort from a prospective, nested case–control study. • 1261 male subjects (mean age: 64 ± 9 y) associations of demographic, clinical, dietary, and laboratory parameters with plasma FGF-23. • Semiquantitative FFQ, blood sample.	Total dietary P(including review of foods commonly enriched with food additives, for example, processed meats and cola beverages)	• Higher P intake was associated with higher FGF-23 levels, independent of other factors. • Higher FGF-23 levels were associated with higher serum P, PTH, uric acid, triglycerides, and lower HDL. • Higher levels of PTH, P, triglycerides, uric acid, and some biomarkers of inflammation were independently associated with higher FGF-23 levels. • Across different FGF-23 levels, there were no differences in frequency of intake of foods enriched with P-based additives.	Low
Kemi and others (2010) 19781123	Low calcium:phosphorus ratio in habitual diets affects serum parathyroid hormone concentration and calcium metabolism in healthy women with adequate calcium intake	• Cross-sectional analysis. • 147 women (age: 31 to 43 y). • Associations between dietary Ca:P intake ratio and S-PTH in women with adequate Ca intake. • 4-d food record, fasting blood samples, and 24-h urine samples.	Total dietary P	• The greatest significant increase in S-PTH and urinary Ca concentrations were observed in subjects in the 1st quartile (lowest Ca:P molar ratio) than in all other quartiles. • Habitual diets with low Ca:P ratios may interfere with homoeostasis of calcium metabolism and increase bone resorption, as indicated by higher S-PTH and urinary Ca levels.	Low
López-Huertas and others (2006) 16469989	Absorption of calcium from milks enriched with fructo-oligosaccharides, caseinophosphopeptides, tricalcium phosphate, and milk solids	• Randomized, controlled, double-blind, crossover trial. • 15 healthy adults (25 to 36 y). • Absorption of Ca from milks enriched with various additives. • 5 types of semiskimmed milk labeled with ^{42}Ca (1 control and 4 Ca-fortified milks) were administered in a randomized order with a light breakfast, separated by a 2-wk washout between each test period (TCP was labeled with ^{44}Ca); volume was adjusted to keep Ca quantities the same between test periods. • 7-d food record collected for 1st test period baseline (and subjects asked to try and maintain similar diet for each subsequent test period), predose and postdose blood samples and 4 d of 24-h urine samples were collected for each test period.	• 5 types of fortified semiskimmed milk • Normal milk (control) • Milk solids and TCP-enriched milk • Caseinophospho-peptide-enriched milk • Fructo-oligosaccharide-enriched milk • Milk concentrate-enriched milk	• Ca absorption from the TCP added to the milk-solid–fortified milk was significantly higher than from the control milk (27.5 ± 7.6% and 24.5 ± 7.3%, respectively; $P = 0.003$). • Ca absorption did not differ significantly between the control milk and the fortified milks.	High

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Heaney (2000) 10966895	Dietary protein and phosphorus do not affect calcium absorption	• Cross-sectional study. • 191 females (48.7 ± 7.0 y). • (567 separate studies over 32 y) • Assessment of whether variations in P and protein intakes were associated with variations in Ca absorption. • Full metabolic balance assessments (using double tracer method to assess Ca absorption), using duplicate diet technique.	Total dietary P	• P and protein intake had no effect on Ca absorption. • Age, body weight, and estrogen status were highly significant predictors of relative absorption of Ca.	Low
Brot and others (1999) 10363752	Relationships between bone mineral density, serum vitamin D metabolites and calcium:phosphorus intake in healthy perimenopausal women	• Cross-sectional study, population-based. • 510 healthy women (age: 45 to 58 y) with amenorrhea. • Followed for 3 to 24 mo. • Assessment of Ca and P intake using 4- or 7-d dietary records.	Dietary P	• Dietary Ca:P ratio was inversely related to serum $1,25(OH)_2D$ ($P = 0.04$) and positively related to BMD ($P < 0.0005$). • No relationships detected between PTH concentrations, serum ionized Ca and phosphate, and serum vitamin D metabolites. • Elevated levels of $1,25(OH)_2D$ were associated with decreased BMD and BMC, reduced Ca:P ratio in the diet, and increased bone turnover.	Low
Barsotti and others (1998) 9647491	Secondary hyperparathyroidism in severe chronic renal failure is corrected by very-low dietary phosphate intake and calcium carbonate supplementation	• Open-label interventional trial. • 21 (12 males, 9 females), chronic uremic patients (serum creatinine: >6.5 mg/dL) with secondary HPT. • Switch from standard low-protein (0.6 g/kg/d), low P (9 to 10 mg/kg/d) diet without vitamin D preparations to study diet for 4 (±2) mo.	• Total dietary P • (very low-protein [0.3 g/kg/d], • low-phosphorus • [5 mg/kg/d] • diet supplemented with essential amino acids, ketoanalogs, and calcium carbonate [2 to 4 g/d])	• Plasma P decreased and calcium increased. • Mean S-PTH decreased by 48%. • Creatinine clearance decreased, and protein catabolic rate was reduced. • Reducing dietary P resulted in significantly reduced S-PTH in patients with severe chronic renal failure who also have secondary HPT.	Low
LOAD OF INGESTED PHOSPHORUS: Associated with physiological outcomes					
Trautvetter and others (2016) 26786148	Consequences of a high phosphorus intake on mineral metabolism and bone remodeling in dependence of calcium intake in healthy subjects—a randomized placebo-controlled human intervention study	• Double-blind, randomized, placebo-controlled, parallel-group trial. • 62 healthy men and women (mean age: 28 ± 6 y to 29 ± 8 y). • 2-wk placebo run-in followed by 8-wk study. • Baseline 24-h urine and fasting blood samples, diets were recorded for 7 d. • Blood and urine, samples were collected before, during, and after the treatment periods. • Fecal samples were collected before and after the treatment periods.	Total dietary P supplemented with 1000 mg/d P (as monosodium phosphate), all arms, and either 0, 500, or 1000 mg/d Ca (as Ca carbonate).	• No differences in the changes in plasma PTH concentrations between the 3 arms. • FGF-23 increased by an average of 17% after 4 wk and decreased 33% at 8 wk for all arms. • Plasma $1,25(OH)_2D$ levels increased in all arms (only statistically significant in 0-mg Ca arm). • Urinary Ca excretion increased at 4 and 8 wk in 0-mg Ca arm. • No significant changes in fasting serum phosphate levels, regardless of Ca dose. • Fecal calcium concentrations were significantly increased after 8 wk in the 500-mg Ca and 1000-mg Ca arms.	High

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Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Goto and others (2014) 24578219	Dietary phosphorus restriction by a standard low-protein diet decreased serum fibroblast growth factor 23 levels in patients with early and advanced stage chronic kidney disease	• Prospective interventional study. • 35 subjects, 15 with early CKD (mean age: 45 ± 13 y) and 20 with advanced CKD (mean age: 66 ± 13 y). • All subjects consumed a regular diet (15 to 20 mg/kg/d of P) for 2 d followed by a low-protein diet (10 to 15 mg/kg/d of P) for 4 to 6 d. • Fasting blood samples and 24-h urine samples were collected on the final day of each diet regimen.	Dietary P	• Serum FGF-23 levels significantly decreased after the low-protein diet regimen (in early CKD, from 52.8 to 38.6 pg/mL; $P = 0.006$). • There was no significant change in S-PTH in the early CKD group. • Serum $1,25(OH)_2D$ significantly increased in the early CKD group (36.0 pg/mL to 47.0 pg/mL; $P = 0.03$). • Serum Ca levels were unchanged. • Urinary P levels significantly decreased.	Low
Vervloet and others (2011) 21030580	Effects of dietary phosphate and calcium intake on fibroblast growth factor-23	• Open-label, crossover study. • 10 healthy adults (23.5 ± 1.6 y). • Effects of high and low phosphate and Ca diets on serum FGF-23, PTH, and vitamin D levels and urinary P excretion. • Administered diet low or high in phosphate and Ca content during 2 study periods of 36 h each, separated by a 1-wk washout period. • Measured serum biochemistry several times daily, 24-h urine samples on all study diet days.	Total dietary P: • Low diet: P (850 mg) and Ca (280 mg) • High diet: P (2880 mg) and Ca (1700 mg)	• For the diet high in P and Ca, there were statistically significant increases in serum P concentration, serum FGF-23 concentration, and urinary P excretion, and there was a statistically significant decrease in S-PTH. • There were no significant changes from baseline in serum Ca concentrations. • Multivariate analysis indicated lower $1,25(OH)_2D$ levels with phosphate/Ca-enriched meals.	Moderate
Obeid and others (2010) 20368708	Increased phosphorus content of preload suppresses ad libitum energy intake at subsequent meal	• Randomized, cross-over study. • 53 adults (age: 17 to 32 y). • Impact of P content in meals on hepatic ATP synthesis and on satiation. • Two chilled preloads were administered at least 1 wk apart in a blinded, randomized order. • Energy intake was measured from a standardized meal served 80 min after preload.	Total dietary P, plus preload solution (with or without 500 mg phosphate)	• Preloads with added P were associated with significant reductions in energy intake at subsequent meals.	High
Shuto and others (2009) 19406976	Dietary phosphorus acutely impairs endothelial function	• Double-blind, crossover study. • 11 healthy men (age: 21 to 33 y). • Flow-mediated dilation of the brachial artery was measured before and 2 h after the meals. • Serum P was measured 8 h after the meals.	Meals containing low (400 mg) or high (1200 mg) P	• Peak serum concentrations for the low P meal occurred at 6 h and for the high meal at 2 h. • The serum P levels after the high meal exceeded the normal range while for the low meal the P level stayed within the normal range. • High dietary P load significantly decreased flow-mediated dilation of brachial artery that normalized after at least 24 h. • No significant correlation between serum P level and flow-mediated dilation was observed after the low meal. • Results suggest that endothelial dysfunction mediated by acute postprandial hyperphosphatemia may contribute to the relationship between serum P level and risk cardiovascular morbidity and mortality.	High

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Kemi and others (2008) 17903344	Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose–response study in healthy females	• Randomized, controlled trial. • 12 healthy female subjects (age: 21 to 40 y). • Three 24-h study sessions, in randomized order, with ≥1 wk between each session; Ca dose of 0 (control day), 600, or 1200 mg/d (subject served as own control). • 24-h urine sample and 5 blood samples collected during each study session.	Total dietary P (identical meals containing 1850 mg P and 480 mg Ca per day)	• PTH concentration decreased ($P < 0.001$) and serum ionized Ca concentration increased ($P < 0.001$) with increasing Ca doses. • The bone resorption marker (U-NTx corrected for creatinine excretion) was significantly decreased by the Ca doses ($P = 0.008$, ANOVA). • When P intake was above current recommendations, increased Ca intake was beneficial for bone, as indicated by decreased S-PTH concentration and bone resorption.	High
Karp and others (2013) 22763799	Mono- and polyphosphates have similar effects on calcium and phosphorus metabolism in healthy young women	• Randomized, controlled trial. • 14 women (age: 19 to 31 y). • 3 doses of MP, PP, or a placebo with meals in randomized order. • Markers of Ca and P metabolism were followed 6 times over 24 h.	MP and PP salts provided 1500 mg P/d	• During both MP and PP sessions, serum phosphate, urinary phosphate, and S-PTH increased. • PP decreased U-Ca more than MP. • Results suggest that PP binds Ca in the intestine more than MP.	Moderate
Karp and others (2007) 17401693	Acute effects of different phosphorus sources on calcium and bone metabolism in young women: a whole-foods approach	• Randomized, controlled trial. • 16 healthy women (age: 20 to 30 y). • Acute effects of dietary P from 3 different food sources and a phosphate supplement on Ca and bone metabolism. • Five 24-h study sessions, in randomized order, with 1 wk between each session (subject served as own control). • 24-h urine sample and 4 blood samples (at 08:00 and 14:00 and immediately after meal at 18:00) collected during each study session.	Total dietary P(control session: 500 mg P, 4 other sessions: 1500 mg P with 1000 mg from meat, cheese, whole grains, or a phosphate supplement)	• Meat and phosphate supplement increased urinary phosphate excretion more than grain or cheese (and control). • Phosphate supplement reduced serum Ca concentration significantly compared with control session (meals with whole grains and meat had no effect on serum calcium compared with control). • Only the phosphate supplement increased S-PTH. • Cheese decreased S-PTH. • The effects of high P intake appeared to depend on the source of P consumed, P from meat and supplements appeared to be absorbed better than P from whole grains.	High
Ito and others (2007) 17968495	Effect of acute changes of serum phosphate on fibroblast growth factor (FGF) 23 levels in humans	• Prospective interventional study. • 4 healthy men. • After overnight fasting, dibasic potassium phosphate dissolved in saline was administered intravenously for 4 h. • Blood samples were collected before infusion and hourly after the start of infusion for 6 h.	Dibasic potassium phosphate	• After infusion, serum phosphate gradually decreased to 3.68 ± 0.62 mg/dL at 6 h. • Phosphate infusion decreased serum Ca: 96.7% ± 0.4% of baseline at 2 h and 94.2% ± 1.0% of baseline at 4 h. • Phosphate infusion increased S-PTH levels: iPTH was 153.9% ± 16.5% of baseline at 2 h and 205.0% ± 24.1% of baseline at 4 h. • Acute changes of serum phosphate did not modify FGF-23 levels in the healthy volunteers.	Moderate
Kakuris and others (2007) 17892762	Phosphate balance in phosphate supplemented and unsupplemented health subjects during and after hypokinesia	• Prospective, interventional study. • 40 healthy men (mean age: 24.2 ± 2.0 y). • Divided into 4 groups: – Unsupplemented active control – Unsupplemented hypokinetic – Supplemented active control – Supplemented hypokinetic	Dicalcium phosphate	• The following increased in hypokinetic subjects during hypokinesia compared with active control subjects: P imbalance, serum Pi and Ca levels, fecal Pi loss, and urine calcium and Pi loss increased in hypokinetic subjects. • Risk of higher P imbalance is directly related to the magnitude of phosphate intake. • During hypokinesia, P imbalance due to the inability of the body to use P but not due to a shortage of P in the diet.	Moderate

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Burnett and others (2006) 16869716	Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women	• Randomized, controlled trial. • 66 healthy adults (age: 18 to 45 y). • 2500-kcal diet randomized to either phosphate-depleted or phosphate-loaded diets for 5 d, after a 4-d run-in diet.	• Days 1 to 4: diet contained 900 mg of phosphate • Days 5 to 9: protein content was decreased and contained 500 mg of phosphate • The phosphate-loaded group received 2500 mg (500 mg from the diet and 2000 mg from supplements)	• Serum P levels were significantly reduced after phosphate deprivation but there were no differences in serum P levels. after dietary phosphate loading. • Evidence suggests that reducing phosphate intake reduces serum phosphate levels. • There was not enough evidence to determine the effects of phosphate loading on serum phosphate. • FGF-23 decreased with of dietary P depletion and increased with load of phosphorus.	High
Kemi and others (2006) 16925861	High phosphorus intakes acutely and negatively affect Ca and bone metabolism in a dose-dependent manner in healthy young females	• Randomized, controlled trial. • 14 healthy women (age: 20 to 28 y). • Short-term effects of 4 P doses on Ca and bone metabolism. • 4 study days in randomized order with 1 wk between sessions; P dose of 0 (placebo), 250, 750, or 1500 mg/d administered in 3 equal doses (subjects served as own control). • 24-h urine sample and 6 blood samples obtained during each study session.	Total dietary P (identical meals containing 495 mg/d P plus randomized dose of P supplement)	• Significant dose response relationship between serum P doses ($P = 0.0005$). • Serum Ca concentrations decreased in response to P intake ($P = 0.0005$) but was significant only after the 1500 mg P dose ($P = 0{\cdot}004$). • P doses affected the S-PTH in a dose-dependent manner ($P = 0.0005$). • Urinary P excretion increased in a dose-dependent manner with increasing P doses ($P = 0.0005$). • Load of P intake was inversely associated with serum concentrations of biomarkers of bone formation. • Significant decline in serum BALP activity after the 750- and 1500-mg P doses.	High
Nishida and others (2006) 17063170	Acute effect of oral phosphate loading on serum fibroblast growth factor 23 levels in healthy men	• Randomized, double-blind, crossover trial. • 8 healthy men (mean age: 22.75 y). • Investigation of whether FGF-23 mediates in the rapid regulation of phosphorus homeostasis. • Subjects consumed test lunch meals, containing different amounts of phosphorus, in a randomized order (400, 800, and 1200 mg per meal). • Postprandial blood and urine samples collected for 8 h after meal.	Total dietary phosphorus (test meals containing 400, 800, or 1200 mg phosphorus)	• Serum FGF-23 levels were decreased or not changed up to 6 h after all diets, but modestly increased at 8 h after the highest phosphorus meal. • Serum phosphorus concentrations increased as phosphorus intake increased. • Cumulative urinary phosphorus excretion was significantly increased in response to phosphorus loading. • Statistically significant negative association between FGF-23 and serum P, positive association between FGF-23 and renal P reabsorption rate. • The S-PTH levels were significantly associated with both serum P levels and renal P reabsorption rate. • FGF-23 may not be involved in the rapid regulation of P homeostasis, but FGF-23 may act as a phosphaturic factor.	High

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Antoniucci and others (2006) 16735491	Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men	• Open-label, crossover trial. • 13 healthy men (age: 28 to 43 y). • To investigate whether serum FGF-23 concentration is regulated by dietary P and thereby mediates the physiological response of serum $1,25(OH)_2D$ to changes in dietary P. • Standard diet administered over 4 wk, addition of P supplements (9 d per dose) in a specified order. • Blood was drawn in the morning fasting state during the last 2 d of each study period, and urine was collected throughout the last 24 h of each study period.	• Total dietary P (constant diet of 500 mg/d P • plus P supplement to achieve total daily dose: control = 1500 mg/d; supplemented = 2300 mg/d; restricted = 625 mg/d)	• Serum $1,25(OH)_2D$ concentrations were significantly greater during P restriction and lowest with P supplementation. • Serum FGF-23 levels decreased significantly during P restriction. • FGF-23 concentrations were 57% higher during supplemented compared with restricted P and 32% higher during control compared with restricted P. • Serum iPTH was significantly decreased when P intake was restricted and was significantly increased when dietary P was supplemented. • Urinary P excretion increased with supplemented P and decreased with restricted P. • Urinary Ca excretion varied directly with dietary phosphorus intake ($P < 0.001$). • Changes in dietary P within the physiological range of intakes regulate serum FGF-23 concentrations. • Dietary P regulation of $1,25(OH)_2D$ production is mediated, at least in part, by changes in circulating FGF-23.	Moderate
Ditscheid and others (2005) 15987849	Cholesterol metabolism is affected by calcium phosphate supplementation in humans	• Randomized, placebo-controlled, double-blind, crossover study. • 31 young healthy adults (mean age: 25 ± 2 y). • Amorphous CaP incorporated into bread; 1060 mg Ca and 490 mg P added to 140 g bread, as compared with unsupplemented placebo bread. • Each crossover period lasted 4 wk.	Pentacalcium hydroxytriphosphate (supplemented in bread)	• Serum cholesterol concentrations decreased significantly ($P = 0.008$) after 4 wk of supplementation. • Excretion of cholesterol increased ($P = 0.025$), while excretion of the cholesterol metabolite coprostanol decreased ($P = 0.025$).	High
Zorbas and others (2002) 11934246	Phosphate deposition capacity of athletes during hypokinesia, phosphate loading, and ambulation	• Randomized, controlled trial. • 40 male athletes (mean age: 24.7 ± 8 y). • Assessed metabolic evaluations for 30 d and phosphate deposition over a 1-y period. • Subjects were randomized into 4 groups: (1) active unsupplemented control, (2) unsupplemented hypokinetic. (3) active supplemented control, and (4) supplemented hypokinetic group.	CaP load (85-mg/kg load)	• Urinary Ca and P loss, fecal P loss, serum phosphate, and serum Ca levels increased significantly ($P \leq 0.05$) in the supplemented hypokinetic group compared with the supplemented active group. • Urinary Ca and P loss, fecal P loss, serum phosphate, and serum Ca levels increased significantly ($P \leq 0.05$) in the unsupplemented hypokinetic group compared with the unsupplemented active group.	High
Martinez and others (1997) 9100037	The importance of dietary calcium and phosphorus in the secondary hyperparathyroidism of patients with early renal failure	• Prospective, interventional study. • 157 patients with chronic renal failure. • P restriction (10 d) followed by P loading (10 d), with or without Ca supplementation.	Dietary P	• Dietary protein and P restriction, together with calcium supplementation, improved HPT. • After P restriction, S-PTH decreased only in subjects with Ca supplementation ($P < 0.03$). • After P load, S-PTH increased ($P < 0.006$). • Phosphate load diet worsened HPT, regardless of Ca supplementation.	Low

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Kärkkäinen and Lamberg-Allardt (1996) 8970892	An acute intake of phosphate increases parathyroid hormone secretion and inhibits bone formation in young women	• Randomized, controlled trial. • 10 females in Part 1. • 10 females in Part 2. • Part 1: single dose of 1500 mg P in water, or placebo. • Part 2: 3 doses of P (500 mg each) in water, or placebo. • Ca and bone metabolism markers were measured for 24 h.	P supplementation	• Serum phosphate increased in both Part 1 ($P = 0.00005$) and Part 2 ($P = 0.0005$). • Serum iPTH concentration increased in both Part 1 ($P = 0.0083$) and Part 2 ($P = 0.014$). • Serum carboxy-terminal PICP decreased in Part 1 ($P = 0.04$), and BALP activity decreased in both Part 1 and Part 2 of the study ($P = 0.027$ and $P = 0.026$, respectively). • There was no significant change in serum BGP, while ICTP and urine DPD were unaffected by phosphate administration. • Results suggest that phosphate administration may lead to an acute inactivation of the early phases of bone formation.	High
Portale and others (1996) 8638697	Effect of aging on the metabolism of phosphorus and 1,25-dihydroxyvitamin D in healthy men	• Prospective interventional study. • 16 men (7 with mean age of 71 ± 1 y and 9 with mean age of 29 ± 2 y). • A constant whole food diet provided 550 mg P, 170 mg Ca, 85 mg Mg, and 80 meq sodium per 70 kg body weight for 26 d. • P intake was altered orally as a solution of neutral sodium and potassium phosphate.	Dietary P (normal, then increased and decreased within normal range)	• At each intake of P, serum concentrations of $1,25(OH)_2D$ was not significantly different in elderly men but decreased by 16% in young men ($P < 0.05$). • Fasting and 24-h mean serum P concentrations were lower in elderly men. • When dietary P was restricted, serum $1,25(OH)_2D$ increased by 47% in elderly men and 46% in young men, and 24-h mean serum P decreased by 0.6 ± 0.1 mg/dL in both groups; serum concentrations of $1,25(OH)_2D$ varied inversely with 24-h mean serum P ($r = -0.92$; $P < 0.0001$). • Irrespective of dietary intake of P, mean serum $1,25(OH)_2D$ levels were in elderly men were not statistically significantly different from that in young men.	Moderate
Galloway and others (1996) 8820890	The effects of acute phosphate supplementation in subjects of different aerobic fitness levels	• Randomized, controlled trial. • 12 healthy men. • 6 trained cyclists (high fitness group). • 6 untrained individuals (low fitness group). • Blood was drawn before treatment, during submaximal exercise, during recovery, and at exhaustion. • Cardiorespiratory variables monitored during exercise.	Dibasic CaP or Ca carbonate (placebo)	• Low-fitness group had higher plasma phosphate concentrations before treatment. • No treatment effects on plasma phosphate were noted at any sample time in either group. • Phosphate ingestion had no effects on blood 2,3-diphosphoglycerate, plasma lactate, oxygen uptake, oxygen pulse, minute ventilation, time to exhaustion or maximal oxygen consumption (VO_{2max}). • Acute dibasic CaP supplementation did not affect aerobic performance; aerobic fitness level did not affect response to phosphate supplementation.	Moderate
FOOD-ADDITIVE PHOSPHATE CONTENT IN DIET: Associated with clinical outcomes					
Ma and Jones (2004) PMID: 15549642	Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: a population-based case–control study	• Case–control study. • 206 cases (single fracture site) and 206 controls. • Children (9 to 16 y). • Evaluating association of soft drink and milk drink consumption and fractures. • Food frequency assessment (average intake of milk drinks, colas, and carbonated beverages in a normal week over the past year).	Milk and soft drinks	• Colas, but not total carbonated beverage consumption, were associated with increased wrist and forearm fracture risk (association was not independent of other factors and appeared to be mediated by television watching and BMD but not by decreased milk intake). • Total intake of carbonated beverages and milk was not associated with fracture risk.	Low

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Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Wyshak (2000) 10850510	Teenaged girls, carbonated beverage consumption, and bone fractures	• Cross-sectional, retrospective study. • 460 teenage girls (mean age: 15 y). • Evaluated association between carbonated beverage consumption and fracture risk in teenage girls. • Questionnaire assessed whether carbonated beverages were consumed and what type (no frequency information).	Carbonated beverage (subcategorized by colas and noncolas)	• Bone fractures were associated with carbonated beverage intake for all girls: OR = 3.14 (95% CI: 1.45, 6.78); $P = 0.004$. • Risk of bone fractures was highest in active girls who consumed cola and noncola carbonated beverages: OR = 7.00 (95% CI: 2.00 to 24.46); $P = 0.002$. • Risk of bone fractures for all girls who drank colas: 2.7 (95% CI: 1.30 to 5.60); $P = 0.008$	Low
TOTAL PHOSPHORUS CONTENT IN DIET: Associated with clinical outcomes					
Wilson and others (2015) 25527761	Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study	• Prospective cohort study of the HPFS. • 47885 men (age: 40 to 75 y). • Assessed association between Ca and P intake and prostate cancer. • Semiquantitative FFQ.	Total dietary P (also subdivided by food products)	• P intake was associated with greater risk of total and high-grade prostate cancers, independent of Ca and intakes of red meat, white meat, dairy, and fish. • Higher P intake was associated with increased risk of advanced-stage and high-grade disease 0 to 8 y after exposure.	Low
Merritt and others (2015) 25662427	Investigation of dietary factors and endometrial cancer risk using a nutrient-wide association study approach in the EPIC and Nurses' Health Study (NHS) and NHSII	• Prospective cohort study. • Associations between endometrial cancer and intakes of 84 foods and nutrients in EPIC study; tested in 2 validation cohorts: NHS and NHSII. • EPIC: 301107 women (age: 25 to 70 y) • NHS and NHSII: 155406 women (age: 25 to 55 y). • FFQs.	Total dietary P (also categorized by food types)	• 2834 cases of endometrial cancer evaluated. • In EPIC, 10 of 84 food/nutrients were associated with risk of endometrial cancer including P (HR: 0.93; 95% CI: 0.73 to 1.19). • Associations with endometrial cancer for 8 dietary factors, including P, were not confirmed in NHS and NHSII.	Low
Ruel and others (2014) 23931982	Association between nutrition and the evolution of multimorbidity: the importance of fruits and vegetables and whole grain products	• Prospective cohort over 5 y. • 1020 adults in China (mean age: [±SD]: 49 [13] y). • Evaluated weighted 3-d food records for association of nutrients at baseline and evolution of morbidity of 11 chronic diseases (multimorbidity).	Total dietary P (also categorized by food types)	• Prevalence of multimorbidity increased from 14% to 34% over 5 y. • Mean P intakes decreased with increasing multimorbidity. • Increasing consumption of fruits, vegetables and grain products other than rice and wheat was associated with healthier stages in the evolution of multimorbidity.	Low
Chang and others (2014) 24225358	High dietary phosphorus intake is associated with all-cause mortality: results from the NHANES III	• Prospective cohort study. • 9686 healthy nonpregnant adults (20 to 80 y). • Median 14.7 y follow-up. • 24-h dietary recall.	Total dietary P (also categorized by food types)	• Median P intake: 1166 mg/d. • Median P density: 0.58 mg/kcal. • Greater P consumption associated with higher all-cause mortality with P consumption >1400 mg/d. • Higher P density was associated with increased all-cause mortality and CV mortality risk at amounts >0.35 mg/kcal. • All-cause mortality associated with the highest quartile of dietary P intake did not vary with soda consumption, fast food consumption, or the United States Department of Agriculture Healthy Eating Index score. • Higher serum P concentration was itself associated with increased mortality. • High P intake was associated with increased mortality in a sample of individuals representative of the healthy population in the United States.	Low

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Lin and others (2014) 24656162	Association of dietary calcium, phosphorus, and magnesium intake with caries status among schoolchildren	• Cross-sectional study. • 2248 school children in Taiwan (age: 6 to 12 y). • Evaluated 24-h dietary recalls, food frequency, and dental examination.	Total dietary P	• No association was detected between dental caries and dietary P intake. • Ca:P ratio was inversely associated with caries in both primary teeth (OR = 0.52; $P = 0.02$) and in permanent teeth (OR = 0.59; $P = 0.02$).	Low
Ramezani Tehrani and others (2013) 23451261	Intake of dairy products, calcium, magnesium, and phosphorus in childhood and age at menarche in the Tehran Lipid and Glucose Study	• Prospective cohort study. • 134 prepubertal girls (4 to 12 y at baseline). • Association between dairy product, Ca, Mg, and P intakes and early onset of menarche (age: ≤12 y). • 24-h dietary recall.	Total dietary P(also categorized by dairy product types)	• Earlier menarche in girls with higher intakes of P, Ca, and Mg. • P intake >647 mg/d was associated with early menarche (OR: 3.43; 95% CI: 1.45 to 8.13; $P = 0.005$). • Prepubertal intake of milk may hasten age at menarche.	Low
Murtaugh and others (2012) 21810769	Dietary phosphorus intake and mortality in moderate chronic kidney disease: NHANES III	• Prospective cohort study. • 1105 adults with early-stage III CKD selected from NHANES III. • Association between dietary P intake and mortality in moderate CKD. • 24-h dietary recalls.	Total dietary P	• No statistically significant association of intake tertile with mortality. • Statistically significant increase in serum P concentration associated with increasing dietary phosphorus intake. • P intake was not associated with death (HR = 0.98 per 100 mg/dL increase; 95% CI: 0.93 to 1.03).	Low
Kesse and others (2006) 16512941	Dairy products, calcium and phosphorus intake, and the risk of prostate cancer: results of the French prospective SU.VI.MAX (Supplémentation en Vitamines et Minéraux Antioxydants) study	• Prospective cohort study 2776 men (age: 45 to 60 y). • Association between dairy product, Ca, and P intake and risk of prostate cancer. • 24-h dietary record.	Total dietary P (analyzed by total and specified dairy products source)	• RR for prostate cancer in the highest (>1434 mg/d) compared with the lowest (<1167 mg/d) quartile of P intake was 1.83 (95% CI: 0.89 to 3.73); $P = 0.04$ for trend across all quartiles. • Risk of prostate cancer increased with increasing Ca intake, only statistically significant for Ca from dairy sources. • For dairy products, only higher consumption of yogurt showed a statistically significant association with increased risk of prostate cancer in the multivariate analysis. • Noted a positive relationship between Ca intake and the risk of prostate cancer, which may be modulated by P intake.	Low
Tseng and others (2005) 15883441	Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort	• Prospective cohort. • 3612 men (age: 25 to 74 y). • Association between dairy, Ca, P, and vitamin D intakes and prostate cancer risk. • FFQ and 24-h recall.	Total dietary P (analyzed by total and specified dairy product source)	• No association detected between dietary P intake and prostate cancer risk when Ca was also considered. • Strong association between dairy food intake and prostate cancer risk, and between dietary Ca intake and prostate cancer risk.	Low
Tavani and others (2005) 15967248	Dietary intake of calcium, vitamin D, phosphorus, and the risk of prostate cancer	• Case–control study. • 1294 men with prostate cancer, and 1451 male controls (age: 46 to 74 y). • Associations between Ca, vitamin D, and P intakes and risk of prostate cancer. • FFQ.	Total dietary P	• No evidence for association between dietary intake of phosphorus and prostate cancer risk.	Low
Kesse and others (2005) 15880532	Dietary calcium, phosphorus, vitamin D, dairy products, and the risk of colorectal adenoma and cancer among French women of the E3N-EPIC prospective study	• Prospective cohort study. • 73034 women (age: 40 to 65 y). • 2 parts: – 4804 polyp free controls – 172 colorectal cancer compared with 67312 controls • FFQ.	Total dietary P	• Increased intake of P was associated with a decrease in risk for all adenomas (RR: 0.70 [95% CI: 0.54 to 0.90]; $P = 0.005$) for trend across all quartiles. • Similar trends for high-risk adenoma and for colorectal cancer but these were not statistically significant.	Low

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Sharkey and others (2003) 12663282	Summary measure of dietary musculoskeletal nutrient (calcium, vitamin D, magnesium, and phosphorus) intakes is associated with lower-extremity physical performance in homebound elderly men and women	• Cross-sectional study. • 321 homebound, elderly adults (≥60 y). • Associations between lower-extremity performance score (calculated from measures of static and dynamic balance) and summary musculoskeletal nutrient score (calculated from quartiles of intake for Ca, vitamin D, Mg, and P). • 24-h dietary recall.	Total dietary P	• OR (95% CI) for the worst level of lower-extremity physical performance for persons in the lowest category of musculoskeletal nutrient scores was 1.88 (1.08 to 3.27) when compared with the OR in the highest nutrient score category ($P \leq 0.05$). • The mean (±SD) percentage of RDA of P in the diet of subjects was 161.6% (±46.3%) for men and 124.8% (±39.2%) for women.	Low
Chan and others (2000) 11075876	Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland)	• Prospective cohort study (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study). • 27062 male smokers (50 to 69 y). • FFQ.	Total dietary P	• No association of dietary P and total prostate cancer risk in a standard multivariate model. • Adjusted multivariate RR for Stages 2 through 4 prostate cancer for highest quintile of dietary P intake was 1.1 (95% CI: 0.7 to 1.8; $P = 0.45$ for trend) across all quintiles. • Men with lower Ca and higher P intake (11% of study population) had a RR of 0.6 (95% CI: 0.3 to 1.0; $P = 0.09$) as compared with men with lower intakes of both nutrients.	Low
Michaud and others (2000) 11130620	Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in U.S. men	• Prospective cohort study. • 47909 men (40 to 75 y). • Evaluated the relationship of intakes of macro- and micronutrients, and the risk of bladder cancer. • FFQ.	Total dietary P	• No association was observed between macronutrient intake and bladder cancer.	Low
Scott and others (2010) 21054294	Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study	• Prospective cohort study • 740 older adults (age: 50 to 79 y). • Associations between dietary nutrient intake, including P, and muscle mass and strength. • FFQ.	Total dietary P	• Appendicular lean mass at baseline was associated with dietary P intake in the multivariate analysis. • Change in appendicular lean mass was associated with dietary P intake (both before and after adjustment for protein intake). • No associations were demonstrated between energy-adjusted nutrient intake and muscle strength.	Low
Elmståhl and others (1998) 10024903	Increased incidence of fractures in middle-aged and elderly men with low intakes of phosphorus and zinc	• Prospective cohort study. • 6576 males (age: 46 to 68 y). • Associations between low dietary intakes of zinc and P and risk of fracture. • 7-d menu book and FFQ.	Total dietary P	• Energy-adjusted P intake in the lowest quintile (mean level: 1357 mg) was associated with an increased fracture risk compared with the risk of fracture in subjects in the 2nd quintile. • Observed lack of a dose–response relationship between dietary P intake and fracture risk, with an apparent threshold effect.	Low
Chan and others (1998) 10189041	Dairy products, calcium, phosphorus, vitamin D, and risk of prostate cancer (Sweden)	• Case–control study. • 526 cases (mean age: 70.7 y), 536 controls (mean age: 70.6 y). • Associations between dietary intake and prostate cancer incidence in men newly diagnosed with prostate cancer and randomly selected age-matched controls. • FFQ assessed 68 foods in Swedish diet • Cancer screening. • Enrolled men (age: <80 y) with newly diagnosed prostate cancer.	Total dietary P (focus on specific dairy, meat, grain, fruit, and vegetable foods)	• Multivariate RR = 0.67 (95% CI: 0.44 to 1.02) for highest quartile of dietary phosphorus intake relative to lowest quartile. • For a continuous measure, dietary phosphorus intake not associated with risk of prostate cancer ($P = 0.22$). • Consumption of dairy foods associated with a higher risk of prostate cancer; calcium, in conjunction with phosphorus, possibly a critical component in this association.	Low

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Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Boutron and others (1996) 8679449	Calcium, phosphorus, vitamin D, dairy products, and colorectal carcinogenesis: a French case–control study	• Case–control study. • 1269 adults (age: 30 to 75 y). • 2 parts: • –362 adenoma cases, 426 polyp-free controls • –171 cancer cases, 309 controls • Associations between intakes that evaluated risks of Ca, P, vitamin D, and dairy products and colorectal carcinogenesis, adenoma and colorectal cancer. • Diet-history method.	Total dietary P (focus on total and specified dairy products)	• High dietary intake of P or low Ca:P ratio was not associated with increased risk of adenomas. • OR of 1.9 for colorectal cancer with highest quintile of dietary P intake, OR = 1.9 (95% CI: 0.8 to 4.6; $P = 0.17$ for trend across all quintiles) for colorectal cancer. • Trend toward an increased risk of colorectal cancer associated with P intake). Trend higher in women (OR: 3.5; CI: 0.8 to 15.9; *P* for trend 0.08), but not in men (OR: 1.4; CI: 0.4 to 4.7).	Low
LOAD OF INGESTED PHOSPHORUS: Associated with target organ effects or biomarkers					
Grimm and others (2001) 11305263	High phosphorus intake only slightly affects serum minerals, urinary pyridinium crosslinks, and renal function in young women	• Prospective, interventional study. • 10 healthy women (age: 23 to 29 y). • Study divided into 3 diet periods: (1) 1700 mg P and 1500 mg Ca per day for 4 wk, (2) 3008 mg P and 1995 mg Ca per day for 6 wk, and (3) 1700 mg P and 1500 mg Ca per day for 4 wk (washout period). • Blood samples were collected at the beginning of the study, at the end of each study period, and in the middle of the supplementation period.	Dietary P, supplemented	• All subjects reported intestinal distress throughout the P-supplementation period. • There were no changes in serum levels of Ca, phosphate, or zinc. • Despite high P supplementation (3008 mg P per day for 6 wk), no significant changes in bone-related hormones, pyridinium crosslinks as markers of bone resorption, and parameters of renal function were shown.	Low
PHOSPHORUS BALANCE (ABSORPTION/EXCRETION): Associated with change in serum phosphorus concentration					
Ix and others (2014) 25332338	Effect of dietary phosphate intake on the circadian rhythm of serum phosphate concentrations in chronic kidney disease: a crossover study	• Crossover feeding study. • 11 CKD subjects and 4 healthy controls (mean age: 64 ± 14 y). • Diet with high, normal and low P (from natural food sources) for 5 d, followed by a 10-d washout. • After each 5-d feed, phosphate and other measurements were made every 4 h for 24 h.	• High-phosphate (2500 mg/d) • Normal-phosphate (1500 mg/d) • Low-phosphate (1000 mg/d)	• Circadian pattern of serum phosphate observed in healthy and CKD with lowest concentrations at 08:00 and highest at 16:00 and 04:00. • The magnitude of change in phosphate is blunted in CKD relative to healthy subjects. • Differences in serum phosphate concentrations comparing low- and high-phosphate diets in had smallest differences at 08:00 and the largest difference at 16:00. • Overall, a circadian pattern of serum P concentration was observed in CKD and could be modified by P intake.	Low
PHOSPHORUS BALANCE (ABSORPTION/EXCRETION): Associated with target organ effects or biomarkers					
Chang and others (2013) 23810691	Association of a reduction in central obesity and phosphorus intake with changes in urinary albumin excretion: the PREMIER study	• Observational study to reduce obesity. • 481 adults with normal kidney function who provided adequate 24-h urine collections at baseline and 6 mo to measure UAE.	Dietary P	• After 6 mo, the proportion of individuals with UAE ≥10 mg/d decreased. • Decreases in UAE were associated with decreases in 24-h urine P and decreases in waist circumference. • Decreases in waist circumference and 24-h urine P are associated with reductions in UAE.	Low
PHOSPHORUS BALANCE (ABSORPTION/EXCRETION): Associated with clinical outcomes					
Palomino and others (2013) 23539231	24-H Urine Phosphorus Excretion and Mortality and Cardiovascular Events	• Prospective cohort study. • 880 patients (67 ± 11 y) with stable CVD and normal kidney function to moderate CKD. • 24-h UPE and serum P measured at baseline, participants were followed for a median of 7.4 y for CV events and all-cause mortality.	Dietary information not reported for subjects	• There was no statistically significant association of UPE with all-cause mortality irrespective of kidney function.	Low

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Table D1—Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
TOTAL PHOSPHORUS CONTENT IN DIET					
Adatorwovor and others (2015) 26610559	Intakes of Calcium and Phosphorus and Calculated Calcium-to-Phosphorus Ratios of Older Adults: NHANES 2005 to 2006 Data	• Cross-sectional study of 1992 subjects aged ≥50 y from NHANES (2005 to 2006). • Dietary intake collected using two 24-h recall questionnaires and supplement intake collected for last 30 d. • Analyzed to determine Ca, P and Ca:P intake ratio (by mass). • Data categorized by sex and age groups (age: 50 to 70 y and ≥71 y).	Total dietary P	• Intake of Ca was lower and P was higher than the current RDAs. • Amount of phosphate additives in processed foods was not available and actual Ca:P ratio may be lower than observed ratio of 0.7:1.0. • Women had greater Ca:P intake ratio than men in the same age groups, due to higher consumption of Ca supplements and Ca-containing foods, and reduced consumption of P-containing foods.	Low
Navarro-Alarcon and others (2012) 22935340	Duplicate portion sampling combined with spectrophotometric analysis affords the most accurate results when assessing daily dietary phosphorus intake	• Analytical study. • 50 healthy adults, 30 women and 20 men (age: 15 to 75 y). • Assessed daily dietary P intake using 3 techniques: – Spectrophotometric analysis of breakfast, lunch, and dinner – Duplicate portion sampling of 108 hospital meals and food composition tables – 24-h dietary recall and food composition tables	Dietary P	• The mean daily dietary P intake determined by spectrophotometry was significantly lower ($P < 0.001$) than from food composition tables. • The food composition tables overestimated the P content of the meals analyzed. • Duplicate portion sampling plus spectrophotometric analysis afforded the most accurate and reliable results in evaluating phosphate daily dietary intake. • Discrepancies could be attributed to differences in the composition of meals caused by food variability, geographic location, technological and cooking processes, and the underestimation of P additives.	Unrated[c]
Sugiyama and others (2009) 19786381	Average daily intake of phosphorus in 3- to 5-y-old Japanese children as assessed by the duplicate-diet technique	• Observational trial. • 90 children (age: 3 to 5 y). • Duplicate portions of all food and drinks were collected for 3 d (1 d each in summer, autumn, and winter) for spectrophotometric P analysis.	Dietary P	• No significant differences were detected in P intake among the 3, 4 and 5-y age groups, but a difference based on sex was seen ($P < 0.05$). • There was a significant age difference seen in the Ca:P ratio between children aged 3 and 4 y ($P < 0.05$). • There was a significant difference in seasonal daily P intake studied (718 mg/d in summer, 735 mg/d in autumn, and 497 mg/d in winter). • P intake was positively correlated with milk and dairy products, meats, beans and bean products, green and yellow vegetables, hypochromic vegetables, fruits, and sugars.	Low
Welch and others (2009) 19888269	Variation in intakes of calcium, phosphorus, magnesium, iron, and potassium in 10 countries in the European Prospective Investigation into Cancer and Nutrition study	• Observational analysis of 8% of the population in the EPIC study. • Assessed nutrient intakes for 36034 subjects (age: 35 to 74 y). • Used standardized 24-h dietary recall software.	Dietary P	• Women had significantly lower intakes of all nutrients than men ($P < 0.001$). • There were significant decreases in P intake as age increased in 5 out of the 10 countries in the study. • Dairy foods, cereal products, and meat products contributed to 63% to 75% of P intake in all countries.	Low
Sherman and Mehta (2009) 19628683	Phosphorus and potassium content of enhanced meat and poultry products: implications for patients who receive dialysis	• Analytical study to determine P content in food. • Examined the potassium and P contents in a variety of enhanced and regular meat and poultry products from stores in New Jersey. • Measurement of P content was based on the Association of Analytical Communities Official Method 984.27 using atomic spectroscopy procedures.	Dietary P	• Enhanced products had a phosphate-to-protein ratio that was 28% greater than that for regular, nonenhanced products. • Uncooked meat and poultry products that are enhanced may contain additives that increase P content by approximately 2-fold.	Unrated[c]

(*Continued*)

Table D1–Continued

Study reference[a] PMID	Title	Methods	Source of phosphorus	Results and conclusions	Quality rating[b]
Sullivan and others (2007) 17720105	Phosphorus-containing food additives and the accuracy of nutrient databases: implications for renal patients	• Analytical study to determine P content in chicken products. • Study compared the measured P content of 38 chicken products with the amount estimated from dietitian's reference used to advise patients. • The chicken products were prepared and cooked according to package directions. • Samples were shipped to Medallion Laboratories for P content measurements.	Dietary P	• Of 38 chicken products, 35 (92%) had P-containing additives listed among their ingredients. • For every category of chicken products containing additives, actual P content was greater than the content expected from nutrient database. • Available reference sources do not reflect the higher P content, and the variation between similar products makes it impossible for patients and dietitians to accurately estimate P content.	Unrated[c]
Moreno-Torres and others (2001) 11753488	Dietary intake of calcium, magnesium, and phosphorus in an elderly population using duplicate diet sampling compared with food composition tables	• Cross-sectional study. • 112 institutionalized elderly subjects: 87 females and 25 males (mean age: 83 ± 7 y). • Food record method: duplicate diet technique. • 1-wk food duplicate samples. • Minerals analyzed by spectrophotometry.	Total dietary P	• Significant differences ($P < 0.05$) were seen in all of the minerals analyzed (Ca, Mg, and P). • Results suggest that the use of food composition tables is not suitable to evaluate the Ca, Mg, and P in nutritional trials. • Results show that it is essential to consider the differences to establish the adequate intakes of Ca, Mg, and P for the elderly population in relation to the mineral bone status.	Low
Heaney and Nordin (2002) 12074251	Calcium effects on phosphorus absorption: implications for the prevention and cotherapy of osteoporosis	• Retrospective analysis of 2 data sets obtained from 2 centers. • 636 subjects (age: 19 to78 y). • Multiple regression models used.	Dietary P	• Mean net absorption of P was 60.3% (±18.1) for Data Set 1 and 53.0% (±9.4) for Data Set 2. • Fecal Ca and diet P were positively and independently associated with fecal P. • When Ca intake increased without a corresponding increase in P intake, P absorption fell, and the risk of P insufficiency increased.	Low
Zhang and others (1999) 10201805	Estimates of mineral intakes using food composition tables compared with measures by inductively coupled plasma mass spectrometry: Part 1. calcium, phosphorus and iron	• Cross-sectional study. • 884 adult nonsmoking women in 6 areas of Asia. • Analysis of 24-h food duplicate samples. • Daily nutrient intake (Ca, P, and iron) was estimated using established food composition tables.	Dietary P	• Comparison of estimated values with measured values were highly variable. • Deviation between estimated and measured values of P was 113% to 306%. • Estimates using food composition tables of dietary intakes differ from the results of instrumental analysis.	Low
Szajkowski (1996) 9008833	Magnesium, calcium, and phosphorus contents in daily food rations in primary school children: questionnaire and analytic studies	• Cross-sectional cohort. • 24 children, 12 boys and 12 girls (age: 9 to 14 y). • Used questionnaire to document foods consumed during the previous 24 h (7 d of a week for 4 seasons of a year). • Simulated meal components were mineralized and were subjected to spectrophotometric P analysis.	Dietary P	• Daily intake of P exceeded recommended daily requirements. • Studied food rations did not meet recommended daily intake of Mg and Ca. • Authors concluded: inadequate Ca:Mg and Ca:P ratios deserve special concern as they may create health hazards for the studied school children.	Low

$1,25(OH)_2D$, 1,25-dihydroxycholecalciferol (= 1,25 dihydroxyvitamin D); AI, augmentation index; ALP, alkaline phosphatase; BALP, bone-specific alkaline phosphatase activity; ANOVA, analysis of variance; ARIC, Atherosclerosis Risk in Communities Study; ART, antiretroviral therapy; ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; ATP, adenosine triphosphate; BAL, bone-specific alkaline phosphatase; BGP, osteocalcin; BMC, bone mineral content; BMD, bone mineral density; BMI, basal metabolic index; BP, blood pressure; Ca, calcium; Ca:P, calcium to phosphate ratio; CAC, coronary artery calcification; CAD, coronary artery disease; CaP, calcium phosphate; CARDIA, Coronary Artery Risk Development in Young Adults; CaxPi, calcium and inorganic phosphorus; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; DEXA, dual-energy x-ray absorptiometry; DM, diabetes mellitus; DPD, deoxypyridinoline; DPG, diphosphoglycerate; eGFR, estimated glomerular filtration rate; EPIC, European Prospective Investigation into Cancer and Nutrition; ESRD, end-stage renal disease; FFQ, food frequency questionnaire; FGF-23, fibroblast growth factor 23; FHS, Framingham Heart Study; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HPFS, Health Professionals Follow-Up Study; HPT, hyperparathyroidism; HR, hazard ratio; ICTP, serum carboxy-terminal telopeptide of type I collagen; iFGF-23, intact fibroblast growth factor 23; IMT, intima-media thickness; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MESA, Multi-Ethnic Study of Atherosclerosis; Mg, magnesium; MI, myocardial infarction; MP, monophosphates; MRI, magnetic resonance imaging; MRP, Maillard reaction products; NHANES, National Health and Nutrition Examination Survey; NHANES III, National Health and Nutrition Examination Survey III; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; OR, odds ratio; P, phosphorus; Pi, inorganic phosphorus; PICP, serum carboxy-terminal propeptide of type I collagen; PMID, PubMed identification number; PP, polypohsphates; PTH, parathyroid hormone; RDA, recommended dietary allowance; RR, relative risk; S-PTH, serum parathyroid hormone; SBP, systolic blood pressure; TCP, tricalcium phosphate; TP, total phosphorus; UAE, urinary albumin excretion; U-Ca, urinary calcium; UPE, urine phosphorus excretion; VO_{2max}, maximal oxygen consumption.

[a]Studies are listed in chronologic order under each subheading.

[b]Quality rating of clinical studies:
Low = observational, noninterventional study including case-control, retrospective and cross-sectional or sample-survey designs
Moderate = prospective, interventional or noninterventional cohort studies
High = randomized (blinded or unblinded) controlled clinical trial

[c]Study did not receive a quality rating because the study was not a clinical study.

provide for or against the safety of dietary food-additive phosphate, and accounted, in part, for the numerous inconsistencies among the studies in their findings. Several of the methodological limitations of a study may be inferred from the category to which the publication reporting the study is assigned in Table D1.

For example, publications appearing in Table D1 under the heading "TOTAL PHOSPHORUS CONTENT IN DIET: Associated with change in serum phosphorus concentration" report studies that can potentially contribute to the assessment of the safety and risks of food-additive phosphate only if serum phosphorus concentration is used as a surrogate for, or predictor of, health, morbidity, or mortality: but serum phosphorus concentration has very limited utility in this regard. Only publications classified under the heading "FOOD-ADDITIVE PHOSPHATE CONTENT IN DIET: Associated with Clinical Outcomes" report studies that can potentially support or refute directly the safety of different intakes of dietary food-additive phosphorus. Evidence from all other studies can provide at best only indirect evidence. Each reported clinical study was assigned a quality rating, and these ratings are recorded in the right-most column of Table D1. The rating criteria appear in Note b to the table.

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October 24, 2016

Ms. Michelle Arsenault
National Organic Standards Board
USDA-AMS-NOP
1400 Independence Avenue, SW
Room 2648-So., Ag Stop 0268
Washington, DC 20250-0268

Docket: AMS-NOP-16-0049

RE: Handling Subcommittee – Cumulative Impact of Phosphates in Organic Processed Foods (Discussion Document)

Dear Ms. Arsenault:

Thank you for this opportunity to provide comment on the Handling Subcommittee's discussion document on the cumulative impact of phosphates in organic processed foods.

The Organic Trade Association (OTA) is the membership-based business association for organic agriculture and products in North America. OTA is the leading voice for the organic trade in the United States, representing organic businesses across 50 states. Its members include growers, shippers, processors, certifiers, farmers' associations, distributors, importers, exporters, consultants, retailers and others. OTA's Board of Directors is democratically elected by its members. OTA's mission is to promote and protect organic with a unifying voice that serves and engages its diverse members from farm to marketplace.

Summary of OTA's Position
OTA recognizes that high phosphorous intake may result in a spectrum of health problems for a small segment of the population, particularly for individuals with chronic kidney disease. There is insufficient evidence suggesting overconsumption of phosphates in the broader healthy population. The use of phosphate additives in organic food is actually quite limited and restricted compared to the use of phosphates in non-organic foods. From a health perspective, there is insufficient science indicating that the phosphate additives on the National List should be removed or phased out in the short term. More research is needed. Based on member feedback during the 2017 Sunset Review process (Appendix A) and during this comment period, we are unaware of any allowed alternative substances currently available that fulfill the same function as calcium phosphate (mono, di, and tri), potassium phosphate (for use in "made with organic" products only), sodium acid pyrophosphate (as a leavening agent only) and sodium phosphate (for use in dairy products only). However, as a matter of organic preference and principle, OTA members are interested in and committed to finding and/or developing natural and organic alternatives. OTA encourages NOSB to continue to review phosphates within their currently scheduled five-year Sunset Review process and make relisting determinations based on conclusive evidence supporting OFPA criteria: 1) the availability of alternatives; 2) whether they are harmful to human health and the environment; and 3) whether they are consistent with organic handling. OTA fully supports this process.

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The Handling Subcommittee is asking the following questions:

1. **If some brands of organic processed dairy products can be produced without use of phosphates, why not all of them? What are the alternatives?**

   In the large majority of the organic dairy products that we investigated, sodium phosphates were used only when they were essential and when there were no alternatives.

   The Technical Review states that, "Some companies produce the same or essentially the same organic product both with and without added phosphates. For example: Kraft Macaroni & Cheese Dinner™ is "organic" with added phosphate, and Kraft Organic Cheddar Macaroni & Cheese Dinner™ is produced without added phosphate." Our review of the various brands of Macaroni and Cheese products on the market shelves found this to be the case as well.

   There are several factors than can influence whether sodium phosphate is required. Examples include the type of cheese used (e.g. cheddar, asiago, Monterey jack), the type of equipment used and/or the type of mechanical processing (e.g. spray-drying) used at various stages in the process flow. Consistent with the results of our survey, member feedback expressed the lack of alternative ingredients and/or processing methods that will meet all circumstances. However, efforts to identify alternatives are underway and progress is being made.

   We also found that sodium phosphate is not needed for organic ultra-pasteurized half and half provided the manufacturer is employing a steam injection process. Our understanding is that the large majority of the organic Ultra Pasteurized (UP) half and half in the marketplace is processed using a steam injection process. Some processing facilities, however, may only be equipped with a tubular steam system (heat-exchange) instead of a steam injection system, or the facility may have a steam injection system but smaller runs dedicated to organic production will be run through the tubular system. Due to the high fat content of half and half, the tubular system tends to foul and/or plug the heat exchangers. Fouling is an issue because it reduces heat transfer efficiency and increases pressure drop. As a result of fouling, there is a possibility of deterioration in product quality because the process fluid cannot heat up to the required temperature (for pasteurization or sterilization). Also, the deposits dislodged by the flowing fluid can cause contamination. The di-sodium phosphate is used as a processing aid that prevents the fouling. In this application, if sodium phosphate were to be removed from the National List, organic manufacturers that do not have a steam injection system installed would need adequate time and resources to invest and transition.

2. **If European, Japanese, CODEX and IFOAM standards limit phosphates to only monocalcium phosphate and only as a leavening agent, why are all the other phosphates necessary in U.S. organic food processing?**

   By and large, the type of phosphate most commonly used in organic products is mono-calcium phosphate. This form is allowed in the U.S., Canada, Europe, Japan, IFOAM, Mexico, Taiwan, and South Korea.

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The necessity of other phosphates in the United States is likely due to the cultural differences in food choices and consumer demand. It should be noted that phosphates have had little to no impact on current equivalency arrangements. Phosphates, individually or as a group, have not been singled out as *critical variances. Therefore, they are currently deemed as equivalent under all existing equivalency arrangements (EU, Canada, Korea, Japan, Swiss).

*Critical Variance: Terms that are not accepted under an equivalency arrangement. Under the U.S./EU Equivalency Agreement for example, the EU recognizes the USDA National Organic Program (NOP) as equivalent to the EU Organic Program and allows products produced and certified as meeting USDA NOP standards to be marketed as organic in the EU. Likewise, the U.S. allows European products produced and certified under the EU Organic Program to be marketed as organic in the U.S. provided antibiotics have not been administered to animals. EU organic producers and processors are required to attest that each shipment meets the terms of the arrangement.

3. **Should phosphate food additives in processed organic foods be phased out, and if so, should just some of them be phased out or should it be allowed in only some products?**

From a health perspective and considering available alternatives, there is insufficient information indicating that any of the phosphate additives on the National List should be removed or phased out in the short term. More research and time are needed. In the long term, OTA supports all efforts to replace allowed synthetic phosphate additives with natural or organic alternatives and/or new processing technologies.

It appears that overconsumption of phosphorous is a food choice issue that results from choosing a diet rich in processed foods, soda and processed meat. From this perspective, it could be expected that phosphorus intake, as a result of the phosphate that is ***added*** to organic food, would be lower in an organic diet because of the fewer number of phosphate additives allowed under the organic regulations and the narrow allowance that is placed on sodium phosphate, sodium acid pyrophosphate and potassium phosphate. For example, the sodium phosphates are commonly used in processed meat products. However, under the organic regulations, they are allowed in dairy products only, so added phosphates are not permitted in any prepared organic meat products. As mentioned earlier, member feedback indicates that efforts are being made to move away from the use of sodium phosphate in dairy products.

Sodium acid pyrophosphate (SAPP), which is allowed only as a leavening agent, presents a much greater challenge with respect to available alternatives. SAPP is distinctly different from the other phosphate-leavening agents on the National List because it is “slow-acting.” The only substances on the National List that are ***slow-acting*** leavening agents are yeast and sodium acid pyrophosphate. Yeast, however, is extremely slow and not appropriate for quick bread applications. Monocalcium phosphate is a fast-acting leavening agent and when used in baking powder, the leavening reaction occurs at room temperature. A slow-acting leavening agent such as SAPP will not activate until baking (heating) occurs. Therefore, if an organic handler wants to make a refrigerated or frozen prepared cereal-based product such as a frozen waffle or a canned refrigerated biscuit dough (both of which require the use of a slow acting leavening agent), the only allowed option available that will work is sodium acid pyrophosphate. Conventional food manufacturers often use sodium aluminum phosphate as a slow-acting leavening agent. However, there are health concerns over aluminum consumption, and sodium aluminum phosphate is not on

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the National List.

While we recognize there are studies that link high phosphorous intake to health problems for a small segment of the population, particularly for individuals with chronic kidney disease, there is insufficient evidence suggesting overconsumption of phosphates in the broader healthy population as a result of added phosphates. There is also a lack of research that looks at phosphorous intake as result of the added phosphates in organic food.

We were unable to find any study that included data from direct comparisons of phosphate levels in organic and conventional (non-organic) products. While the study included in the 2016 Technical Review on Phosphates titled "The prevalence of phosphorus-containing food additives in top-selling foods in grocery stores" did include "additive-free" organic products in their comparisons, they were only represented in six out of the 56 comparisons. No organic products were included as representatives of products containing phosphorus additives, and data on phosphorus levels were not included for specific products. As such, it is impossible to determine the extent to which organic products without phosphate additives are available compared to comparable conventional products containing additives, the difference in total phosphorus levels in any organic and conventional products, and the extent to which phosphate levels differ among conventional and organic products that both contain phosphate additives.

*Leon, J. B., C. M. Sullivan, and A. R. Sehgal. 2013. "The prevalence of phosphorus-containing food additives in top-selling foods in grocery stores." *J Ren Nutr* No. 23 (4):265-270 e2. doi: 10.1053/j.jrn.2012.12.003.

OTA appreciates that this topic has been flagged as a Research Priority because we agree that there are important questions that can be asked that would help determine whether phosphate additives, as they are currently restricted on the National List and used in organic foods, are contributors to today's rising dietary consumption of phosphates and whether they are compatible with organic handling practices. Suggested research topics that might help shape the review of phosphates as we move forward include:

- Cumulative impact of phosphate levels in organic food products compared to non-organic food products;
- Contribution of added food phosphates to total phosphorous intake in an organic diet;
- Contribution of added food phosphates to total phosphorous intake in organic food compared to non-organic food;
- Consumer perception and preference of organic food products containing phosphate additives.

In the meantime, we encourage NOSB to continue to review phosphates within their fiv-year Sunset process and make determinations based on the availability of alternatives, impact to human health and the environment, and whether they are consistent with organic handling.

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On behalf of our members across the supply chain and the country, OTA thanks the National Organic Standards Board for the opportunity to comment, and for your commitment to furthering organic agriculture.

Respectfully submitted,

Gwendolyn Wyard
Vice President, Regulatory and Technical Affairs
Organic Trade Association

cc: Laura Batcha
Executive Director/CEO
Organic Trade Association

Appendix A – 2017 Sunset Survey Results

Calcium phosphates (mono, di & tri)	**Handler Comment:** Used in organic baked goods, specifically as an ingredient in baking powder. Certified for five years and selling products nationwide. Not aware of any alternatives. If this material is removed from the National List, we will no longer sell organic products. Critically essential to our organic products. No alternative. **Handler Comments:** Mono-calcium phosphate is a component of our baking powder, which is used in a wide range of products. There is no other more natural substitute for leavening when yeast is not appropriate. Critical to organic processing. **Handler Comment**: Used for nutrient fortification in gummy bears and other gummy confections.
Potassium phosphates	**Handler Comments:** Used in "Made with organic" nondairy beverages sold in 50 states and other countries. Certified for over 10 years. Buffering agent (pH control) to prevent precipitation and impaired mouth-feel. Tried alternatives but they do not work well. Loss of this material would result in impaired quality and marketability of products and loss of sales. Critically essential.

Sodium phosphates	**Handler Comments:** Used as an emulsifier in organic cheese products. Vital to the operation. No other alternatives are acceptable. We could not make the product without these emulsifiers. We would be unable to produce an organic cheese product. Critically essential. **Handler Comments:** Organic high protein smoothie. Certified for 32 years. The sodium phosphate ionizes in solution, which helps prevent excessive protein-protein interactions in the base that would result in curd formation (interrupts protein gel, stabilizing the texture of the product). No alternatives known. **Handler Comments:** Sodium phosphate Trisodium Phosphate Disodium Phosphate. Used as an emulsifier. We would be unable to produce an organic cheese product. No alternatives. These are vital to the operation
Sodium Acid Pyrophosphates	**Handler Comments:** Pancake mixes as a leavening agent. No alternatives known. Essential to our company. We make our own baking powder to avoid the non-organic (and sometimes non-GMO) pre-blended baking powder on the market. Eliminating this item would hurt us. **Handler Comment:** Cake mixes, cookies. Leavening agent. Other leavening agents don't

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	work as well. We do use cream of tartar and baking soda in certain products, but SAP works better in cake and cookie mixes. Essential to our products. **Handler Comment:** Crackers. Certified for 19 years. leavening agent. Have not explored alternatives

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SCIENTIFIC OPINION

EFSA Journal

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Re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives and the safety of proposed extension of use

EFSA Panel on Food Additives and Flavourings (FAF),
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Abstract

The Panel on Food Additives and Flavourings added to Food (FAF) provided a scientific opinion re-evaluating the safety of phosphates (E 338–341, E 343, E 450–452) as food additives. The Panel considered that adequate exposure and toxicity data were available. Phosphates are authorised food additives in the EU in accordance with Annex II and III to Regulation (EC) No 1333/2008. Exposure to phosphates from the whole diet was estimated using mainly analytical data. The values ranged from 251 mg P/person per day in infants to 1,625 mg P/person per day for adults, and the high exposure (95th percentile) from 331 mg P/person per day in infants to 2,728 mg P/person per day for adults. Phosphate is essential for all living organisms, is absorbed at 80–90% as free orthophosphate excreted via the kidney. The Panel considered phosphates to be of low acute oral toxicity and there is no concern with respect to genotoxicity and carcinogenicity. No effects were reported in developmental toxicity studies. The Panel derived a group acceptable daily intake (ADI) for phosphates expressed as phosphorus of 40 mg/kg body weight (bw) per day and concluded that this ADI is protective for the human population. The Panel noted that in the estimated exposure scenario based on analytical data exposure estimates exceeded the proposed ADI for infants, toddlers and other children at the mean level, and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that phosphates exposure by food supplements exceeds the proposed ADI. The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes.

Keywords: phosphates, phosphorus, food additive, acceptable daily intake, risk assessment, safety

Requestor: European Commission

Question numbers: EFSA-Q-2011-00532; EFSA-Q-2011-00533; EFSA-Q-2011-00534; EFSA-Q-2011-00535; EFSA-Q-2011-00536; EFSA-Q-2011-00537; EFSA-Q-2011-00538; EFSA-Q-2011-00539; EFSA-Q-2011-00540; EFSA-Q-2011-00541; EFSA-Q-2011-00542; EFSA-Q-2011-00543; EFSA-Q-2011-00618; EFSA-Q-2011-00619; EFSA-Q-2011-00620; EFSA-Q-2011-00621; EFSA-Q-2011-00622; EFSA-Q-2011-00623; EFSA-Q-2011-00624; EFSA-Q-2011-00625; EFSA-Q-2011-00626; EFSA-Q-2011-00628; EFSA-Q-2011-00629; EFSA-Q-2011-00630; EFSA-Q-2018-00597.

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* This opinion was first adopted by the FAF Panel on 27 March 2019, as reflected in the minutes of the FAF Panel Plenary Meeting of 27–29 March 2019: http://www.efsa.europa.eu/sites/default/files/event/190326-m.pdf. However, the adopted version was withdrawn prior to publication and the current version was adopted by the FAF Panel on 4 June 2019.

Panel members: Gabriele Aquilina, Laurence Castle, Karl-Heinz Engel, Paul Fowler, Maria Jose Frutos Fernandez, Peter Fürst, Rainer Gürtler, Ursula Gundert-Remy, Trine Husøy, Wim Mennes, Peter Moldeus, Agneta Oskarsson, Romina Shah, Ine Waalkens-Berendsen, Detlef Wölfle and Maged Younes.

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Summary

The present opinion document deals with the re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) when used as a food additive.

Phosphates are authorised food additives in the European Union (EU) in accordance with Annex II and III to Regulation (EC) No 1333/2008 on food additives and specific purity criteria have been defined in the Commission Regulation (EU) No 231/2012. E 338, E 339, E 340 and E 341 are also authorised in food category 13.1 foods for infants and young children.

Phosphates have been previously evaluated by the EU Scientific Committee on Food (SCF, 1978, 1991, 1994, 1997) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1974, 1982a,b, 2002). JECFA concluded that the allocation of an acceptable daily intake (ADI) was not appropriate for phosphates 'as phosphorus is an essential nutrient and unavoidable constituent of food' and it was decided, therefore, to assign a 'maximum tolerable daily intake' (MTDI) rather than an ADI. The MTDI allocated was 70 mg/kg body weight (bw) per day (expressed as phosphorus) for the sum of phosphates and polyphosphates, both naturally present in food and ingested as food additives (JECFA, 1982a). The SCF subsequently agreed with the JECFA MTDI estimate for phosphates and assigned the cations an ADI 'not specified' as they are natural constituents of man, animals and plants (SCF, 1991).

The Expert Group on Vitamins and Minerals (EVM) further concluded that a total intake of 2,400 mg/day (considering 2,110 mg/day inorganic phosphorus from food including food additives and water and 250 mg/day from supplemental phosphorus) does not result in any adverse effects (Expert Group on Vitamins and Minerals, 2003).

In the EFSA NDA Opinion on Tolerable Upper Intake level of phosphorus, the upper level for phosphorus was not established because available data were not sufficient and indicate that normal healthy adults can tolerate phosphorus (phosphates) intake up to at least 3,000 mg/day without adverse systemic effects (EFSA NDA Panel, 2005).

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (VKM) published an assessment of dietary intake of phosphorus in relation to tolerable upper intake levels suggesting 3,000 mg/day as provisional upper level (UL) for total phosphorus intake in adults and 750 mg/day as UL for supplements (VKM, 2017).

Phosphate is essential for all living organisms. Inorganic phosphate used as food additives assessed in this opinion is assumed to dissociate in the gastrointestinal tract. The inorganic phosphorus deriving from food additives is mainly absorbed in the amount of approximately 80–90% as free orthophosphate. Excretion is via the kidney through glomerular filtration and tubular handling.

The Panel considered phosphates to be of low acute oral toxicity and there is no concern with respect to genotoxicity and carcinogenicity.

In standard short-term, subchronic and chronic toxicity studies, the only significant adverse effect of phosphates is calcification of the kidney and tubular nephropathy. In the chronic rat study with sodium triphosphate, the no-observable-adverse-effect level (NOAEL) was 76 mg/kg bw per day phosphorus (Hodge, 1960). Adding the background dietary phosphorus of 91 mg/kg bw per day to the NOAEL of 76 mg P/kg bw per day gives a total value of 167 mg P/kg bw per day.

In studies performed in mice, rats, rabbits or hamsters, there are no signs of reproductive or developmental toxicity at any dose tested. The Panel thus concluded that exposure to phosphates do not present any risk for reproductive or developmental toxicity.

The epidemiological studies reviewed did not find consistent associations between dietary phosphorous intake and cardiovascular-related outcomes and do not provide sufficient and reliable data to assess the role of phosphate on bone health.

Clinical interventional trials in which the doses were given on top of the normal diet were performed over several months. No impairment of the renal function was reported with daily doses up to 2,000 mg phosphorus (28.6 mg/kg per day), whereas doses of 4,800 mg/day (68.6 mg/kg per day) elicited renal impairment. Histopathological examinations of human kidney specimens from exposed patients showed similar findings as seen in animals. In several of the studies using phosphorus doses up to 2,000 mg/day, the subjects had soft stools or diarrhoea which is not to be seen as adverse but is classified as discomfort. However, when higher doses are given, such as the doses for bowel cleansing in preparation for colonoscopy (e.g. 11,600 mg/kg or 165.7 mg/kg bw) these doses acted as a cathartic agent and this effect has to be clearly seen as adverse.

Several case reports indicate that a high acute single dose of phosphate (160 mg/kg bw and more) can induce renal impairment.

The evidence from epidemiological and human interventional studies is not suited to derive an ADI. The Panel therefore selected the 167 mg P/kg bw per day NOAEL identified by Hodge (1960) as the basis to derive the ADI. The chemical-specific adjustment factor for phosphate accounting for interspecies and interindividual differences in toxicokinetics (TK) and toxicodynamics (TD) is $2 \times 2 = 4$. To this value, the phosphorus-specific uncertainty factor of 4 is to be applied resulting in an ADI value of 42 mg/kg bw per day, rounded to 40 mg/kg bw per day.

Currently, phosphates (E 338–341, E 343, E 450–452) are authorised food additives in the EU with maximum permitted levels (MPLs) ranging from 500 to 20,000 mg/kg in 104 authorised uses and at *quantum satis* (QS) in four.

To assess the dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives, the exposure was calculated based on two different sets of concentration data: (1) MPLs as set down in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*).

While analytical data were used to consider the exposure to phosphorus from all dietary sources.

In the context of this opinion, the Panel was in the special situation to assess the safety of food additives, phosphate salts, which are also nutrients. The Panel based its assessment on the toxicity of phosphorus (phosphate moiety). Since the ADI encompasses the phosphorus intake from natural sources and from food additives sources, the usual exposure assessment using the reported use levels of the food additives was not appropriate to characterise the risk linked to the exposure to phosphorus and the exposure assessment was based on analytical data of the total phosphorus content of foods. In this scenario, the exposure exceeds the ADI of 40 mg/kg bw per day in infants from 12 weeks to 11 months, toddlers and children both at the mean and high level. In adolescents, the high level is also exceeding the ADI of 40 mg/kg bw per day.

Based on the reported use levels, the Panel calculated two refined exposure estimates: a *brand-loyal consumer scenario* and a *non-brand-loyal scenario*. The Panel considered that the refined exposure assessment approach resulted in more realistic long-term exposure estimates and that the refined non-brand loyal scenario is the most relevant exposure scenario for the safety evaluation of phosphates. In the *non-brand-loyal exposure assessment scenario*, estimated exposure to phosphates ranged between 1 and 48 mg P/kg bw per day at the mean and between 3 and 62 mg P/kg bw per day at the 95th percentile for all population groups.

The derived ADI 40 mg P/kg bw per day results in a exposure to phosphorus of 2,800 mg/person per day for an adult of 70 kg which is within the safety level of exposure of 3,000 mg/person per day set by the EFSA NDA Panel (2005).

The Panel concluded that the group ADI of 40 mg/kg bw per day, expressed as phosphorus, is protective for healthy adults because it is below the doses at which clinically relevant adverse effects were reported in short-term and long-term studies in humans. However, this ADI does not apply to humans with moderate to severe reduction in renal function. Ten per cent of general population might have chronic kidney disease with reduced renal function and they may not tolerate the amount of P per day which is at the level of ADI.

The Panel noted that in the exposure estimates based on analytical data exceeded the proposed ADI for infants, toddlers and children at the mean level and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that P exposure from food supplements exceeds the proposed ADI.

The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes. When receiving data on the content of contaminants in formula, the Panel noted that the high aluminium content may exceed the tolerable weekly intake (TWI).

The Panel recommends that:

- The EC considers setting numerical Maximum Permitted Level for phosphates as food additives in food supplements.
- The European Commission considers revising the current limits for toxic elements (Pb, Cd, As and Hg) in the EU specifications for phosphates (E 338–341, E 343, E 450–452) in order to ensure that phosphates (E 338–341, E 343, E 450–452) as a food additive will not be a significant source of exposure to those toxic elements in food.
- The European Commission considers revising the current limit for aluminium in the EU specifications for the use of calcium phosphate (E 341).

- The European Commission to consider revising the current EU specifications for calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) to include characterisation of particle size distribution using appropriate statistical descriptors (e.g. range, median, quartiles) as well as the percentage (in number and by mass) of particles in the nanoscale (with at least one dimension < 100 nm) present in calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) used as a food additive. The measuring methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2018).
- The development of analytical methods for the determination of phosphate additives in the range of foods and beverages permitted to contain them should be considered.
- The EFSA Scientific Committee reviews current approaches to the setting of health-based guidance values for regulated substances which are also nutrients to assess if a coherent harmonised strategy for such risk assessments should be devised.

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1. Introduction

The present opinion deals with the re-evaluation of the following food additives: phosphoric acid (E 338), monocalcium phosphate (E 341(i)), dicalcium phosphate (E 341(ii)), tricalcium phosphate (E 341 (iii)), monomagnesium phosphate (E 343(i)), dimagnesium phosphate (E 343(ii)) monosodium phosphate (E 339(i)), disodium phosphate (E 339(ii)), trisodium phosphate (E 339(iii)), monopotassium phosphate (E 340(i)), dipotassium phosphate (E 340(ii)), tripotassium phosphate (E 340(iii)), disodium diphosphate (E 450(i)), trisodium diphosphate (E 450(ii)), tetrasodium diphosphate (E 450(iii)), tetrapotassium diphosphate (E 450(v)), dicalcium diphosphate (E 450(vi)), calcium dihydrogen diphosphate (E 450(vii)), magnesium dihydrogen diphosphate (E 450(ix)), pentasodium triphosphate (E 451(i)), pentapotassium triphosphate (E 451(ii)), sodium polyphosphate (E 452(i)), potassium polyphosphate (E 452(ii)), sodium calcium polyphosphate (E 452(iii)) and calcium polyphosphate (E 452(iv)). For brevity, these food additives will be referred to as phosphates in this document (listed overview of the substances considered in this opinion is available in Appendix A).

As usual in the re-evaluation of food additives, this opinion addresses the safety of phosphorus intake from the use of the above listed food additives in the general population.

During the drafting of the opinion, a request for extension of use has been received and is included in this opinion. The terms of reference are reported below.

1.1. Background and Terms of Reference as provided by the European Commission

1.1.1. Background to the re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives

Regulation (EC) No 1333/2008[1] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010[2]. This Regulation also foresees that food additives are re-evaluated whenever necessary in the light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[3] of 2001. The report 'Food additives in Europe 2000[4]' submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

1.1.1.1. Terms of Reference

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in

[1] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16–33.
[2] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.
[3] COM(2001) 542 final.
[4] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002, 560.

the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

1.1.2. Background to the request for the extension of use of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives

The Directorate-General for Health and Food Safety received a request for the extension of use of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) by removing the restriction 'only sugar confectionary' in the relevant provision in the food category 05.2 'Other confectionary including breath refreshing microsweets'.

1.1.2.1. Terms of Reference

The European Commission requested EFSA to provide a scientific opinion on the safety of the proposed extension of use in accordance with Regulation (EC) No 1331/2008 establishing a common authorisation procedure for food additives, food enzymes and food flavourings and proposed that EFSA incorporates in that risk assessment the assessment of the safety of the proposed extension of use.

1.1.3. Interpretation of Terms of Reference

The former ANS Panel described its risk assessment paradigm in its Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012). This Guidance states, that in carrying out its risk assessments, the Panel sought to define a health-based guidance value (HBGV), e.g. an acceptable daily intake (ADI) (IPCS, 2004) applicable to the general population. ADI is defined as 'an estimate of the amount of a substance in food or drinking water that can be consumed over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight and applies to chemical substances such as food additives, pesticide residues and veterinary drugs'. (EFSA Glossary).

Phosphates are normal constituents in the body and are regular components of the diet. According to the EFSA NDA Panel the available data are not sufficient to establish an upper level (UL) for phosphorus (EFSA NDA Panel, 2005). The EFSA NDA Panel stated in this opinion that 'The available data indicate that normal healthy individuals can tolerate phosphorus (phosphate) intakes up to at least 3,000 mg/day without adverse systemic effects'. In 2015, the NDA Panel set adequate intakes (AIs) values for various age groups.

Inorganic phosphates authorised as a food additive are efficiently absorbed and used systemically. It is noteworthy that although phosphorus is an essential constituent of the human body and other life forms, the element itself always occurs systemically in the oxidation state (V) as free or combined phosphate. It is absorbed and involved in many structural and functional roles as phosphate (HPO^{2-}_4) (see Section 3.5.1). However, dietary and environmental exposure to phosphorus may come from other forms of phosphorus (V). Whereas the systemic physiologically active moiety is phosphate it has become conventional in nutritional and risk assessment as well as regulatory contexts to use inorganic phosphorus as generic the term (Pi). For the purposes of this opinion, phosphorus will be expressed as P. This is particularly necessary in the context of establishing a group ADI which encompasses phosphorus from all sources including all classes of phosphates as food additives (E 338–341, E 343, E 450–452). The mass conversion factors between phosphate and P_2O_5 or P are summarised in Appendix B.

The Panel considered that sodium, potassium, calcium and magnesium salts of phosphate and condensed phosphates are expected to dissociate in the gastrointestinal tract into phosphate and their corresponding cations. The resulting sodium, potassium, calcium and magnesium cations will enter their normal physiological processes. The kinetics of the corresponding cations are not assessed in the opinion.

Data were not always available for all the authorised phosphates for all endpoints but for the reason described above the Panel considered that it is possible to perform read-across between different phosphate additives.

The opinion will also conclude on the proposed extensions of use received during the course of the drafting opinion.

1.2. Information on existing authorisations and evaluations

Phosphates are authorised food additives in the EU in accordance with Annex II and III to Regulation (EC) No 1333/2008[5]. E 338, E 339, E 340, E 341 are also authorised in food category 13.1 foods for infants and young children. Commission Delegated Regulation (EU) 2016/127 and Commission Delegated Regulation (EU) 2016/128, as well as Commission Directive 2006/141/EC and Commission Directive 1999/21/EC, define minimum and maximum levels for phosphorus as well as for the cations of the various phosphate salts (i.e. calcium, potassium and sodium) in the final formula. These statutory requirements are based on the scientific advice by the Scientific Committee on Food (SCF, 1996, 1997, 1998) and EFSA (EFSA NDA Panel, 2013). The minimum and maximum levels of phosphorus for infant formula are set at 25 mg/100 kcal and 90 mg/100 kcal, in the case of infant formula based on soy the maximum level is 100 mg/100 kcal. The minimum and maximum levels for infant formula for special medical purposes are set at 25 mg/100 kcal and 100 mg/100 kcal. In Europe, the phosphates that are permitted as additives in infant formula (category 13.1.1) and foods for infants for special medical purposes (13.1.5.1) are specified in Regulation (EC) No 1333/2008. The permitted level of phosphates used as a food additive, either alone or in combination, is set at a maximum concentration of 1,000 mg/L reconstituted formula. The maximum level is expressed as P_2O_5.

In addition, tricalcium phosphate is authorised, according to Annex III to Regulation (EC) No 1333/2008, for use as food additives in nutrients in infant formula. The maximum carry-over of tricalcium phosphate from nutrients is set at 150 mg/kg as P_2O_5 and within the limit for calcium, phosphorus and calcium:phosphorus ratio as specified in Commission Directive 2006/141/EC. In addition to their use as food additives, calcium, magnesium, potassium and sodium salts of orthophosphoric acid are included in the list of mineral substances which may be used in the manufacture of food supplements reported in the Annex II of Directive 2002/46/EC[6] and in the list of mineral substances which may be added to foods reported in the Annex II of Regulation (EC) No 1925/2006[7].

Calcium, magnesium, potassium and sodium salts of orthophosphoric acid are included in the Union list set out in the Annex to Regulation (EU) No 609/2013[8] as permitted for use in: infant formula and follow-on formula, food for special medical purposes and total diet replacement for weight control. Calcium and magnesium sodium salts of orthophosphoric acid are also permitted for use in processed cereal-based food and baby food.

According to the CODEX STAN 72-1981 on Infant Formula and Formulas for Special Medical Purposes (FSMP) intended for infants, sodium phosphates (339(i), (ii), (iii)) and potassium phosphates (340(i), (ii), (iii)) may be used as additives in infant formula and infant FSMP. The maximum level is specified at 450 mg/L as phosphorus in the ready-to-use product, singly or in combination and within the limits for sodium, potassium and phosphorus (SNE, 2018).

Phosphates have been previously evaluated by the EU SCF (1978, 1991, 1994, 1997) and by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) latest in 1973 and 1982 (JECFA, 1974, 1982a,b).

The toxicology and safety of diphosphates, triphosphates and polyphosphates when used as food additives has previously been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) as part of a larger group of phosphate compounds (JECFA, 1964, 1974, 1982a,b, 1986, 2002). At its 26th meeting, JECFA concluded that the allocation of an ADI was not appropriate for phosphates 'as phosphorus is an essential nutrient and unavoidable constituent of food' (JECFA, 1982a). It was decided, therefore, to assign a 'maximum tolerable daily intake' (MTDI) rather than an ADI. The MTDI allocated was 70 mg/kg bw per day (expressed as phosphorus) for the sum of phosphates and polyphosphates, both naturally present in food and ingested as food additives. 'The lowest level of phosphate that produced nephrocalcinosis in rat (1% P in the diet) is used as the basis for the evaluation and, by extrapolation based on the daily food intake of 2,800 calories, gives a dose level of

[5] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives**.** OJ L 354, 31.12.2008.

[6] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

[7] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

[8] Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009. OJ L 181, 29.6.2013, p. 35–56.

6,600 mg P per day as the best estimate of the lowest level that might conceivably cause nephrocalcinosis in man'. The use of a safety factor was not considered suitable by JECFA with the justification that phosphorous is also a nutrient.

The SCF agreed with the JECFA MTDI estimate for phosphates and assigned the cations an ADI 'not specified' as they are natural constituents of man, animals and plants (SCF, 1991).

In 2012, JECFA evaluated magnesium dihydrogen diphosphate (E 450(ix)) for use as food additive (JECFA, 2012a). In its 76th report, JECFA stated the following: 'The information submitted to the Committee and in the scientific literature did not indicate that the MTDI of 70 mg/kg bw for phosphate salts, expressed as phosphorus, is insufficiently health protective. On the contrary, because the basis for its derivation might not be relevant to humans, it could be overly conservative. Therefore, there is a need to review the toxicological basis of the MTDI for phosphate salts expressed as phosphorus (JECFA, 2012b).

The Expert Group on Vitamins and Minerals (EVM) used as a starting point 750 mg/day; this is the dose that, after oral administration of phosphorus as various phosphate salts, gives osmotic diarrhoea and mild gastrointestinal symptoms in humans. The EVM applied an uncertainty factor of 3 (to allow interindividual variations) to the 750 mg/day and concluded that a supplemental intake of 250 mg/day (3.6 mg/kg bw per day) would not be expected to induce adverse effects (Expert Group on Vitamins and Minerals, 2003). The EVM further concluded that a total intake of 2,400 mg/day (considering 2,110 mg/day inorganic phosphorus from food including food additives and water and 250 mg/day from supplemental phosphorus) does not result in any adverse effects. The exposure calculation in food has been based on a survey from 1986/7 (NDNS 1986/7) which does not include specific estimation of phosphates content in food from food additives.

In the EFSA NDA Opinion on Tolerable Upper Intake level of phosphorus (EFSA NDA Panel, 2005), the upper level for phosphorus was not established because available data were not sufficient, although some adverse gastrointestinal effects have been reported at doses of phosphorus-containing supplements exceeding 750 mg/day. EFSA reported that the mean dietary and supplemental intake of phosphorus in European countries is approximately 1,000–1,500 mg/day and indicate that normal healthy adults can tolerate phosphorus (phosphates) intake up to at least 3,000 mg/day without adverse systemic effects.

In 2015, EFSA published a Scientific Opinion on Reference Values for phosphorus setting adequate intakes (AIs) for all population groups. The AI recommended is 160 mg/day for infants aged 7–11 months, between 250 and 640 mg/day for children and 550 mg/day for adults. The AI for phosphorus has been derived based on the Dietary Reference Values (DRVs) for calcium by using a molar calcium to phosphorus ratio of 1.4:1 (EFSA NDA Panel, 2015).

In 2006, the National Health and Medical Research Council of Australia and the New Zealand Ministry of Health published AIs for infants between 0 and 6 months (Australian Government, NHMRC). The AI of 100 mg/day was calculated by multiplying the average intake of breast milk (0.78 L/day) by the average concentration of phosphorus in breast milk (124 mg/L) from 10 studies reviewed by Atkinson et al. (1995).

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety (VKM) published an assessment of dietary intake of phosphorus in relation to tolerable upper intake levels suggesting 3,000 mg/day as provisional UL for total phosphorus intake in adults and 750 mg/day as UL for supplements (Norwegian Scientific Committee for Food Safety (VKM, 2017)).

2. Data and methodologies

2.1. Data

The Panel on Food Additives and Flavourings (FAF) and its predecessor, the Panel on Food Additives and Nutrient Sources, were not provided with a newly submitted dossier. EFSA, therefore, launched a public call for data[9] and a public consultation.[10] A technical report has been issued by EFSA collecting

[9] Call for technical and toxicological data on phosphates authorised as food additives in the EU. Published: 14 July 2017. Available online: https://www.efsa.europa.eu/en/data/call/170615

[10] Questions for health professionals in the fields of nephrology, mineral metabolism, cardiovascular and nutrition medicine on phosphates food additives re-evaluation. Published: 1 June 2018. Available online: https://www.efsa.europa.eu/en/consultations/call/180601

the answers received in response to the public consultation. All answers received were considered in the development of this opinion.

For the re-evaluation, the Panel based its assessment on information submitted to EFSA following the public calls for data, the public consultation, information from previous evaluations and additional available literature up to 18 March 2019. Attempts were made at retrieving relevant original study reports on which previous evaluations or reviews were based however these were not always available to the Panel.

Following the request for additional data on particle size sent by EFSA on 18 September 2018, one of the Interested Parties requested a clarification teleconference, which was held on 4 October 2018.

An applicant has submitted a dossier in support of the application for the extension of use of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as a food additive which is also addressed in this opinion (Documentation provided to EFSA n. 1).

The EFSA Comprehensive European Food Consumption Database (Comprehensive Database[11]) was used to estimate the dietary exposure.

The Mintel's Global New Products Database (GNPD) is an online resource listing food products and compulsory ingredient information that are included in labelling. This database was used to verify the use of food additive (E 338, E 341(i), E 341(ii), E 341(iii), E 343(i), E 343(ii) E 339(i)), (E 339(ii), E 339(iii), E 340(i), E 340(ii), E 340(iii), E 450(i), E 450(ii), E 450(iii), E 450(v), E 450(vi), E 450(vii), E 450(ix), E 451(i), E 451(ii), E 452(i), E 452(ii), E 452(iii) and E 452(iv) in food products.

2.2. Methodologies

This opinion was formulated following the principles described in the EFSA Guidance on transparency with regard to scientific aspects of risk assessment (EFSA Scientific Committee, 2009) and following the relevant existing guidance documents from the EFSA Scientific Committee.

The FAF Panel assessed the safety of phosphates as food additives in line with the principles laid down in Regulation (EU) 257/2010 and in the relevant guidance documents: Guidance on submission for food additive evaluations by the SCF (2001) and taking into consideration the Guidance for submission for food additive evaluations in 2012 (EFSA ANS Panel, 2012).

On 31 May 2017, EFSA published a guidance document on the risk assessment of substances present in food intended for infants below 16 weeks of age thus enabling EFSA to assess the safety of food additives uses in food for infants below 12 weeks of age (EFSA Scientific Committee, 2017). Therefore, the current evaluation also addresses the safety of use of food additives for all age groups, including the infants below 12 or 16 weeks of age following the principles outlined in that guidance.

When the test substance was administered in the feed or in the drinking water, but doses were not explicitly reported by the authors as mg/kg bw per day based on actual feed or water consumption, the daily intake was calculated by the Panel using the relevant default values as indicated in the EFSA Scientific Committee Guidance document (EFSA Scientific Committee, 2012a) for studies in rodents or, in the case of other animal species, by JECFA (2000). In these cases, the daily intake is expressed as equivalent. When in human studies in adults (aged above 18 years) the dose of the test substance administered was reported in mg/person per day, the dose in mg/kg bw per day was calculated by the Panel using a body weight of 70 kg as default for the adult population as described in the EFSA Scientific Committee Guidance document (EFSA, 2012a).

Dietary exposure to phosphates from their use as food additives was estimated combining food consumption data available within the EFSA Comprehensive European Food Consumption Database with the maximum levels according to Annex II to Regulation (EC) No 1333/2008[12]. Reported use levels and analytical data submitted to EFSA following a call for data were used to assess exposure under different scenarios(see Section 3.3.1). Uncertainties on the exposure assessment were identified and discussed.

Dietary exposure for infants (0–16 weeks) from infant formula and from foods for special medical purposes (FSMP) was calculated based on the minimum and maximum content as defined in the Commission Delegated Regulation (EU) 2016/127 and Commission Delegated Regulation (EU) 2016/128, as well as Commission Directive 2006/141/EC and Commission Directive 1999/21/EC and the reference values on the energy requirements of infants in the first months of life (EFSA NDA Panel, 2013, 2014).

For the assessment of epidemiological studies, a systematic approach has been taken and the protocol is provided in the Appendixes C and D. In addition, the answers received in response to the

[11] Available online: http://www.efsa.europa.eu/en/food-consumption/comprehensive-database

[12] Commission Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

Public Consultation have been considered for the interpretation of the epidemiology studies. It should be noted that because this opinion is dealing with general population, studies focussing on subpopulations with specific health conditions (e.g. patients with moderate to severe decreased renal function) were not considered.

3. Assessment

3.1. Technical data

3.1.1. Chemistry of phosphates

All phosphorus oxoacids and anions have POH groups in which the hydrogen atom is ionisable (Cotton and Wilkinson, 1972). The principal acid is orthophosphoric acid and its various anions. The phosphate ion carries a −3 formal charge and is the conjugate base of the hydrogen phosphate ion, HPO_4^{2-}, which is the conjugate base of $H_2PO_4^-$, the dihydrogen phosphate ion, which in turn is the conjugate base of H_3PO_4, phosphoric acid. Linear polyphosphates are salts of the anions of general formula $[P_nO_{3n+1}]^{(n+2)-}$. Examples are $M^I_4P_2O_7$, (where M represents the associated cation) diphosphate (also named pyrophosphate), and $M^I_5P_3O_{10}$, a tripolyphosphate. Cyclic phosphates are salts of anions of general formula $[P_nO_{3n+1}]^{n-}$. Examples are $M_3P_3O_9$, a trimetaphosphate, and $M_4P_4O_{12}$, a tetrametaphosphate.

The sodium, potassium and ammonium orthophosphates are all water-soluble. Most other phosphates (including magnesium and calcium) are only slightly soluble or are insoluble in water. As a rule, the hydrogen and dihydrogen phosphates are slightly more soluble than the corresponding non-hydrogenated phosphates. The pyrophosphates are mostly water-soluble. Aqueous phosphate exists in four forms: in strongly basic conditions, the phosphate ion (PO_4^{3-}) predominates. Phosphoric acid is tribasic: at 25°C, pK1 = 2.15, pK2 = 7.1 and pK3 ≅ 12.4. In weakly basic conditions, the hydrogen phosphate ion (HPO_4^{2-}) is prevalent. In weakly acidic conditions, the dihydrogen phosphate ion (H_2PO^{4-}) is most common. In strongly acidic conditions, trihydrogen phosphate (H_3PO^4) is the main form. H_3PO_4, HPO_4^{2-} and H_2PO^{4-} behave as separate weak acids because the successive pK values differ by more than 4. The region in which the acid is in equilibrium with its conjugate base is defined by pH ≈ pK ± 2. Thus, the three pH regions are approximately 0–4, 5–9 and 10–14.

A general structural formula of basic structure of ortho and condensed phosphates is given in Figure 1.

Annex 1 of EU 1333/2008 describes the range of additive functional classes which have been summarised in Appendix A for phosphates as described in JECFA Monographs (JECFA, 2018).

Organic phosphates in different forms are also present in the diet and differ considerably in the physico-chemical and physiological properties from inorganic phosphates.

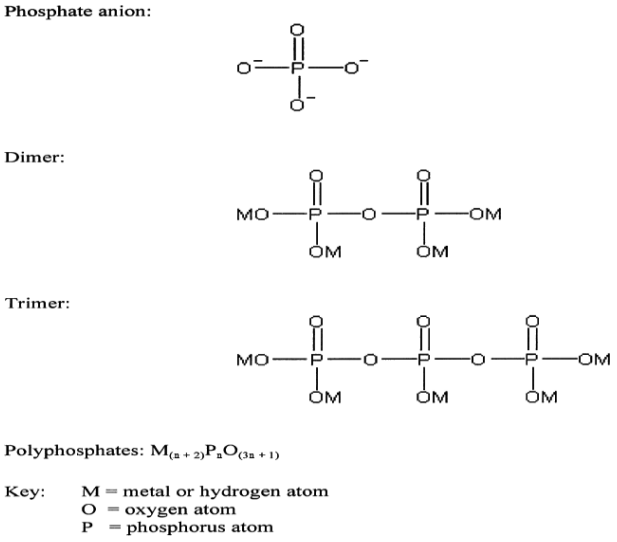

Figure 1: Example of basic structure of ortho- and condensed phosphates taken from Weiner et al. (2001)

3.1.2. Specifications

The identity of substances description and specifications for phosphates as defined in the Commission Regulation (EU) No 231/2012 and by JECFA are listed in Appendix E.

The Panel noted that, according to the EU specifications for phosphates impurities of elements arsenic, cadmium, lead and mercury are each permitted up to a concentration of 1 mg/kg. Contamination of phosphate additives at such levels could have a significant impact on the exposure to these metals, for which the exposure already are close to the HBGVs or benchmark doses (lower confidence limits) established by EFSA (EFSA CONTAM Panel, 2009a,b, 2010, 2012a,b,c, 2014).

The Panel noted that in EU specifications for E 343(i) the chemical name monomagnesium dihydrogen monophosphate has to be corrected.

When considering the information submitted by the industry on the actual aluminium content in infant formula (final food), the Panel noted that the amount of aluminium may result in an exceedance of the respective tolerable weekly intake (TWI) (Documentation provided to EFSA n. 2,3,4,5).

The Panel noted that the use of calcium phosphate (E 341), for which maximum limits for aluminium have been set in the EU specifications, can contribute to the total aluminium content in infant formula.

3.1.3. Particle size

Industry (Documentation provided to EFSA n. 6) provided information on the particle size distribution (volume-based (Dv) values) of calcium dihydrogen phosphate (E 341(i)) (n = 3), calcium hydrogen phosphate (E 341(ii)) (n = 6), tricalcium phosphate (E 341(iii)) (n = 7), dimagnesium phosphate (E 343(ii)) (n = 2) and calcium dihydrogen diphosphate (E 450(vii)) (n = 2) analysed by five laboratories using dynamic light scattering (DLS). One of the laboratories indicated that the sample feeding took place by vibrating plate. The lower Dv50 values were reported for six out of the seven samples of E 341(iii) (around 5 μm) while for the other sample the Dv50 value range from 33 to 92 μm (STD = 22). The major difference in the Dv50 value was observed between the two analysed samples for (E 343(ii)), for one was around 7 μm (STD = 0689) and for the other ranged from 152 to 196 μm (STD = 18).

Additional information of the analysis of other samples of calcium dihydrogen phosphate (E 341(i)) (n = 3), calcium hydrogen phosphate (E 341(ii)) (n = 5), tricalcium phosphate (E 341(iii)) (n = 6), dimagnesium phosphate (E 343(ii)) (n = 3) and calcium dihydrogen diphosphate (E 450(vii)) (n = 3) by transmission electron microscopy (TEM), scanning electron microscopy (SEM) and DLS was submitted (Documentation provided to EFSA n. 7). Median minimum Feret diameter values were reported among other parameters for SEM and TEM.

The lower median minimum Feret diameter values were reported for E 341(iii) (ranged from 2 to 7 μm) using SEM. A big variability on the median minimum Feret diameter values was observed between the analysed samples of E 341(i) (ranged from 3 to 150 μm) using SEM. Similar observations were noted for the results reported by TEM. Before the microscopic analyses, the samples were applied at the adhesive carbon tape by gently tapping of the SEM stub with the applied adhesive tape on top of the appropriate sample. According to the authors, this approach allowed them to observe the particles and their aggregates/agglomerates in the native form.

SEM imagines were post-processed considering a uniform rectangular grid (49–196 nodal points) and only the particles or particles aggregates/agglomerates in the nodal-points were analysed. The Panel noted that the point counting methodology tends to give biased results since large particles have more chance to be selected for measurement than the small. In addition, for some samples magnification should be higher to allow precise measurement.

As indicated in the report, in the TEM images only the particles with well detectable boundaries were analysed. The Panel noted that the magnification used did not allow to identify if there are or not smaller particles.

The same samples were analysed by DLS and number-based (Dn) values were reported (Documentation provided to EFSA n. 6). Dn10 values for some of the samples of E 341(ii), E 341(iii), E 343(ii) and E 450(vii) were around 140 nm.

Based on the available information, the Panel cannot exclude that particles in the nanorange can be present in phosphates when used as a food additive.

3.1.4. Manufacturing process

Information was submitted by CEFIC – Phosphoric Acid and Phosphates Producers Association (PAPA) in response to the public call for data.

Phosphoric acid and salts

Phosphoric acid is produced commercially by two main methods, either a wet process or an electrothermal process. In the wet process, phosphate rock is digested with a mineral acid (usually sulfuric acid, but nitric or hydrochloric acids may also be used). A filtration step then separates the 'wet' phosphoric acid from the insoluble calcium sulfate slurry. As variable amounts of inorganic impurities may be present depending on the origin of the phosphate rock the phosphoric acid is purified through a solvent extraction purification process to produce the food-grade additive. In the electrothermal process, the phosphate rock, coke and silica are first heated in an electric resistance furnace to more than 1,100°C to extract elemental phosphorus from the ore. The elemental phosphorus is then oxidised to P_4O_{10} (phosphorus pentoxide) and subsequently hydrated and the mist is collected. This process produces a high-purity orthophosphoric acid due to the use of pure phosphorous for combustion and only the impurity arsenic needs to be removed in an additional purification step involving treatment with excess hydrogen sulfide and filtration of the precipitate (Documentation provided to EFSA n. 8).

Calcium and magnesium phosphates are produced commercially from phosphoric acid and either calcium oxide or calcium hydroxide, and either magnesium oxide or magnesium hydroxide, respectively. The raw materials are mixed together and the product is separated via centrifugation or filtration. The product is a solid that undergoes further physical treatment (drying, milling, sieving) before being passed through a metal detector and then packaged (Documentation provided to EFSA n. 9,10). No further information on purity requirements for the Ca and Mg containing starting materials were provided.

Both mono- and disodium phosphates are prepared commercially by neutralisation of phosphoric acid using sodium carbonate or sodium hydroxide. Crystals of a specific hydrate can then be obtained by evaporation of the resultant solution within the temperature range over which the hydrate is stable. For the preparation of trisodium phosphate, sodium hydroxide must be used to reach the high pH because carbon dioxide cannot be stripped readily from the solution above a pH approaching 8. Similarly, the potassium phosphates are produced by successive replacement of the protons (H^+) of phosphoric acid with potassium ions.

Diphosphates

The three sodium diphosphates are produced commercially by the neutralisation of phosphoric acid with sodium hydroxide. Solutions of the two reagents are mixed in the required proportions for the specific product (1:1 sodium hydroxide:phosphoric acid for E 450(i); 3:2 for E 450(ii); and 2:1 for E 450(iii)). After reaction, the solution is filtered to remove insoluble impurities. The solution is spray-dried or passed through a rotary kiln or drum dryer. Temperatures greater than 200°C are used; as well as evaporating the water, this temperature promotes a condensation reaction between phosphate groups to produce the diphosphate. The solid material produced is milled, sieved or ground, passed through a metal detector and packaged. Information on manufacturing of tetrasodium diphosphate (E 450(iv)) is missing.

Tetrapotassium diphosphate is manufactured in a similar way, using potassium hydroxide and phosphoric acid. A higher temperature of 350–400°C is used to dry the product and promote the condensation of phosphate groups. The solid product is processed in the same way as described above.

Dicalcium diphosphate is produced from anhydrous dicalcium phosphate (calcium hydrogen phosphate, $CaHPO_4$). The dicalcium phosphate is calcined in a drum drier, rotary kiln or kneader drier at 350–400°C, under which conditions a condensation reaction occurs between phosphate groups. The coarse granules formed are milled, sieved, passed through a metal detector and bagged.

Calcium dihydrogen diphosphate is made in a similar way to the above, but the starting material is monocalcium phosphate ($Ca(H_2PO_4)$). This is calcined in a drum drier, rotary kiln or kneader drier at 270–350°C, where condensation between phosphate groups occurs. The solid product is treated in the same way as described in the above paragraphs.

Magnesium dihydrogen diphosphate (E 450(ix)) is manufactured by adding an aqueous dispersion of magnesium hydroxide slowly to phosphoric acid, until a molar ratio of approximately 1:2 (Mg:P) is

achieved. The temperature is held at 60°C during the reaction. Approximately 0.1% hydrogen peroxide is added and the resulting slurry is heated and milled (Documentation provided to EFSA n. 7).

Triphosphates

Pentasodium triphosphate and pentapotassium triphosphate are produced commercially by the neutralisation of phosphoric acid with sodium or potassium hydroxide, respectively. The neutralised mixture is dried via spray-drying or by being passed through a drum dryer or rotary kiln at temperatures above 250°C. The phosphate produced (di-, tri- etc) depends on the degree of neutralisation and the temperature and residence time in the dryer or kiln. The coarse granules formed are usually milled, sieved, passed through a metal detector and then bagged.

Polyphosphates

The thermal dehydration of monosodium phosphate can give a number of condensed polyphosphates. The particular products formed depend on the conditions used – temperature, water vapour and tempering. Heating NaH_2PO_4 to above 620°C and quenching rapidly gives Graham's salt, a water-soluble polyphosphate glass with a composition of $(NaPO_3)_x$ (where x = 4–1.1). The glass consists of around 90% high molecular weight polyphosphates, with the rest being made up of various cyclic metaphosphates. In contrast, the dehydration of NaH_2PO_4 at 260–300°C produces the low temperature form of Maddrell's salt, $(NaPO_3)_n$ – III, insoluble metaphosphate III. Further heat treatment of this at 360–430°C produces a second form of Maddrell's salt, insoluble metaphosphate II (also $(NaPO_3)_n$). The potassium compound, Kurrol's salt, is similarly obtained by thermal dehydration of KH_2PO_4. No information on manufacturing of E 452(iii) sodium calcium polyphosphate and E 452(iv) calcium polyphosphate.

3.1.5. Methods of analysis in food

Introduction

A variety of analytical methods have been used for the determination of phosphate additives in foods and beverages. So-called 'classical' methods are generally only useful for total phosphate but have been modernised for current applications in some areas. Modern methods such as ion chromatography (IC), capillary zone electrophoresis (CZE) and nuclear magnetic resonance spectroscopy (NMR) can separate, identify and quantify different phosphate types but are not be able to differentiate between added and naturally occurring phosphates. Moreover, most methods suffer from lack of information on natural variation of phosphate levels where only a few useful but limited reviews are available.

Plasma spectrometry is a useful tool for the estimation of the total phosphorus content. Upon comparing IC with direct current plasma spectrometry (DCP), IC can only provide information on ionic phosphates while DCP can allow the determination of all forms of phosphorus. However, a combination of the two techniques can provide a powerful tool for separating, identifying and measuring all forms of phosphorus (Urasa and Ferede, 1986).

The measurement of added phosphates in food products is not straightforward due to the presence of several types of phosphate additives (i.e. poly, tri-, pyro-, orthophosphates). The quantification of phosphate alone cannot be used to verify the presence of added phosphates due to the presence of naturally occurring phosphates and other phosphorus-containing components such as phospholipids and phosphoproteins. For example, there is ca. 0.1–4.8% naturally occurring phosphates in seafood (Campden, 2012); hence, there is a need to distinguish between natural phosphates, which are not well defined, and added phosphates. In addition, there is the issue of stability since polyphosphates are readily hydrolysed to pyrophosphates and (eventually) to orthophosphates due to phosphatase activity (temperature-dependent), processing conditions and during analysis (Scharpf and Kichline, 1967; Das et al., 2011; Campden 2012).

Extraction procedures for phosphates are sample-specific and therefore vary across foods and beverages permitted to contain phosphate additives. Certain extraction conditions (e.g. acids) can also promote the degradation of polyphosphates to orthophosphates.

Indirect methods

Indirect methods for estimation phosphate content are essentially restricted to moisture content and protein content. The ratios of moisture:protein and phosphate:protein can provide useful information on added phosphates. However, the moisture contents of foodstuffs vary greatly and protein measurement relies on the use of interim nitrogen factors following Kjeldahl analysis. While

these methods can show when phosphates and/or water have been added, their accuracy is questionable due to natural variation in phosphate content of foodstuffs (Campden, 2012).

Direct methods

Phosphate may be determined in meat samples using digestion with a mixture of hydrochloric and nitric acids, followed by filtration and treatment with quimociac reagent to form precipitates of quinolinium phosphomolybdate, which are then filtered, washed, dried and quantified gravimetrically (USDA, 2009).

Spectrophotometric methods

Direct analysis of phosphate in foodstuffs is commonly carried out using spectrophotometric (colorimetric) methods, e.g. by measuring the intensity of colour resulting from the interaction of orthophosphates with reagents such as molybdenum blue, yellow vanamolybdate complex and malachite green (Þórarinsdóttir et al. (2010); Campden, 2012). Colorimetric analysis requires the decomposition of poly-, tri- and other forms to orthophosphates achieved through the use of strong acids such as trichloroacetic acid (TCA) and sulfuric acid (H_2SO_4). The total phosphate content is usually expressed as P_2O_5 and therefore does not distinguish between different classes of phosphate additive. A spectrophotometric method has been developed that is able to distinguish between phosphorus due to water-soluble (i.e. inorganic) from organic phosphorus sources such as phospholipid and phosphoprotein (Cupisti et al., 2012). An adaptation of this method can be used to distinguish between orthophosphate and condensed polyphosphates (Þórarinsdóttir et al., 2010). The condensed forms react much more slowly, so measurements are made at 15 and 90 min and the difference between the results is the amount of the condensed forms. The method described above cannot distinguish between the di-, tri- and polyphosphates.

Modern spectrophotometric methods have good sensitivity and precision, which is important because of the natural variation in total phosphates content in foodstuffs. McKie and McCleary (2016) developed and validated a novel and rapid method for the determination of total phosphorus and phytic acid in foods and animal feeds. The method involves the extraction of phytic acid followed by dephosphorylation with phytase and alkaline phosphatase, and measured colorimetrically using a modified molybdenum blue assay. Such methods are used for determining the phosphate content of fertilisers and for assessing the purity of phosphate food additives (JECFA, 2018; EU, 231/2012). The Association of Official Analytical Chemists (AOAC) method describes a standard colorimetric method for the determination of orthophosphate in water (AOAC, 1997). Method details are summarised in Table 1.

Chromatographic methods

Thin-layer chromatography (TLC) methods for determining phosphates are relatively simple and cheap and can separate poly-, tri-, pyro- and orthophosphates. Quantitative estimates of phosphates content can be achieved by comparing colour intensities of spots with standard phosphate solutions. The main disadvantage of TLC is the hydrolysis *in situ* of phosphates during sample extraction and analysis (Campden, 2012). Without additional analysis, TLC is essentially a qualitative technique and it has been shown that false-negative results can arise. For example, where polyphosphates have completely hydrolysed to orthophosphates and are no longer detectable as a distinct species, while similar observations during the TLC analysis of white shrimp, where the limit of detection was estimated at 0.08% (w/w) sodium triphosphate (Campden 2012).

High-performance liquid chromatography (HPLC), or more accurately IC, has been shown to be a useful method for the determination of individual polyphosphates and other phosphate species. IC can separate and quantify poly-, tri-, pyro- and orthophosphates. Post-column colorimetric and conductivity detection can be used to provide sensitive and selective performance with good linear range. IC methods can be used for the simultaneous determination of condensed phosphates including orthophosphates (P1), diphosphates (P2) and polyphosphates (P3 and greater).

Examples of the application of IC in fish, shellfish and crustacea may be found in Campden (2012). A similar methodology has been used IC has been used to determine phosphate species in sausage (Dionex 2010) and for the determination of polyphosphates in fish, shrimp and cuttlefish, and on commercial products of cooked ham, wurstel, corned beef, processed cheese and fish (Iammarino and Di Taranto, 2012). IC has been used recently for the rapid and automated determination of orthophosphate in carbonated soft drinks (De Borba and Rohrer, 2018). Method details are summarised in Table 1.

Electrophoretic methods

Capillary electrophoresis (CE) is a family of related techniques used to separate charged particles based on their size to charge ratio when an electric current is applied (Campden, 2012). The most commonly used technique is capillary zone electrophoresis (CZE), where separation is based on differences in solute size and charge at a given pH. In capillary isotachophoresis (cITP), samples are loaded into a capillary set between two electrolytes (leading and terminating), whereupon the analytes are separated into discrete zones between the electrolytes according to their electrophoretic mobility. Both techniques, either alone or in combination, have been used to detect added phosphates in foodstuffs. Detection techniques include conductivity, fluorescence or ultraviolet (UV). CZE/cITP with conductivity detection has been used to determine phosphate in meat, canned meat products, ham, smoked ham, sausages, paté, prawns, squid and mixed seafood (Jastrzębska, 2009, 2011; Campden 2012). Method details are summarised in Table 1. The clear advantages of using CZE/cITP methods is that they can determine different phosphate species (ortho, di- and tri-) simultaneously and rapidly, requiring a relatively small amount of sample. While results have been reported to be sensitive, accurate and precise the importance of robust sample preparation is requisite. Sample inhomogeneity and the presence of protein and fat can decrease method precision.

Nuclear magnetic resonance (NMR)

^{31}P NMR has been used generally as a research tool rather than as a routine analytical procedure but this technique is becoming more widely available and affordable. ^{31}P NMR can differentiate simultaneously between different phosphate types and is quantifiable. It has been applied to fish and meat products with adequate sensitivity (Campden, 2012). Method details are summarised in Table 1. The results obtained by ^{31}P NMR are reported to more accurate and precise compared to those obtained using the molybdovanadate yellow spectrophotometric method (Szłyk and Hrynczyszyn, 2011).

The issue of polyphosphate degradation notwithstanding, non-destructive, simultaneous observation of different phosphate species is clearly an analytical advantage. Moreover, ^{31}P NMR it has been used to measure total phosphates or polyphosphates but cannot be used to distinguish between natural and added compounds.

Ion chromatography

Upon comparing IC with DCP, IC can only provide information on ionic phosphates while DCP can allow the determination of all forms of phosphorus. However, a combination of the two techniques can provide a powerful tool for separating, identifying and measuring all forms of phosphorus (Urasa and Ferede, 1986).

Other methods

Much less widely used techniques for phosphate determination include thermal differential photometry and microwave dielectric spectroscopy, which are essentially research tools that are not readily applicable to routine analysis of foodstuffs. X-ray fluorescence has also been used (Documentation provided to EFSA n. 7) although is not a widespread technique.

Standard methods and norms

There are few validated official methods available. Those identified to date are summarised with standard methods listed by BVL (2018) in Table 1. The scope of these methods covers ortho-, condensed and polyphosphate analytes, and most foodstuffs and beverages apart from those for infants (e.g. infant formula). Analytical techniques are essentially limited to TLC and/or spectrophotometry, except for IC which is specified for the analysis of soft drinks. Data provided by CEFIC-PAPA provide evidence for the accuracy and precision requirements of standard methods for phosphate determination. For example, the total phosphorus is calculated as g/100 g reported to two significant figures (Documentation provided to EFSA n. 11).

Table 1: Reference methods listed by BVL (2018) and available standard methods

E number(s)	Method number, name, origin	Analyte(s)	Analytical technique	Matrices
BVL methods				
450–452	L 06.00-15 L 07.00-20 L 08.00-22	Condensed phosphates	Thin-layer chromatography	Meat, meat products, processed meats, bakery wares
450–452	L 06.00-9	Di-, Tri-, Poly-Phosphate	Spectrophotometry	Foodstuff, e.g. meat products, fish products, dairy, bakery products, grain-based foods
450(i–vii)	L 06.00-15 ISO-Norm 5553	Diphosphate	Thin-layer chromatography	Dairy, meat products, fish products
451(i, ii)	L 06.00-15 ISO-Norm 5553	Triphosphate	Thin-layer chromatography	Dairy, meat products, fish products
452(i–iv)	L 06.00-15 mod. Iso-Norm 5553 (qualitative) L 06.00-09 mod. (quantitative)	Di-, Tri-, Poly-Phosphate	Thin-layer chromatography Spectrophotometry	Meat products, dairy (cheese, processed cheese), fish products
338–341, 343,450–452	Photometric determination of phosphate after acid digestion in drinks	Total phosphate as PO_4	Spectrophotometry	Soft drinks
338–341, 343,450–452	L 06.00-9	Total phosphate as P_2O_5	Spectrophotometry	Meat, meat products, cheese, dairy
338–343, 450, 451	Condensed phosphates L 06.00-15	Condensed phosphates	Qualitative chromatography	Meat and meat products
338–343, 450, 451	Total phosphorus content L 06.00-9	P_2O_5	Spectrophotometry	Meat and meat products
338–343, 450, 451	Total phosphorus content L 03.00-17	Phosphorous	Spectrophotometry	Cheese, processed cheese, processed cheese preparations
339(i–iii)	L 06.00-15 mod	Triphosphate	Thin-layer chromatography	Fish products
340(i–iii)	Not specified	Phosphoric acid	Ion chromatography	Soft drinks
338	L 31.00-6	Phosphate	Spectrophotometry without ashing	Soft drinks
Other standard methods/norms				
BSI 4401-15:1981/ISO 5553;1981. Methods of test for meat and meat products. Detection of polyphosphates (by spectrophotometry)				
PD ISO/TS 18083:2013. Processed cheese products. Calculation of content of added phosphate calculated as phosphorus (by spectrophotometry)				
AOAC, 1997. Standard colorimetric method for the determination of orthophosphate in water (by spectrophotometry)				

The scope of methods for the determination of phosphates in foodstuffs must cover the complete range of foods and beverages permitted to contain phosphate additives and must be readily applicable in laboratories, i.e. not unnecessarily complex or costly.

While quantitative spectrophotometric methods provide sufficient sensitivity and ease of use, they are limited in scope to the detection and measurement of phosphates in the ortho form, i.e. di-, tri- and polyphosphates must be hydrolysed first to orthophosphates. Hydrolysis may be achieved chemically and/or enzymatically but it will not be possible to discriminate between phosphates present naturally and phosphate additives (however, the latter are likely to be present at a much higher concentration relative to natural phosphates). Published spectrophotometric methods therefore require

further development to encompass all foodstuffs within the required scope, especially with respect to extraction and isolation techniques.

Since spectrophotometric methods cannot be used qualitatively to identify different phosphate additive species, the use of more sophisticated techniques that can separate, identify and quantify different phosphate species is required. Of the available methods, IC is the most widely used but to date, has not been applied to the full range of foodstuffs permitted to contain phosphate additives. For the simultaneous determination of condensed phosphates using IC, systems employing a mobile phase comprising KOH (or NaOH) and macroporous divinyl benzene/ethylvinyl benzene stationary phase run under gradient elution conditions with suppressed conductivity detection, are the most widely reported. In order to reduce the reporting of false positive and/or false negative results, it is recommended that sample preparation times should be as short as possible and should include steps to deactivate phosphatase enzymes.

Appropriate analytical methods must be developed and validated to recognised international protocols so that they are fit for purpose with respect to expected phosphate concentration ranges (i.e. ranging from ca. 500 to 50,000 mg/kg, as well as *quantum satis*). Some foodstuffs have 'no limit defined'. There should also be clear distinction between methods for total phosphate and methods for identifying and quantifying separate phosphate types, i.e. methods must be robust, and the units used for reporting phosphate content should be standardised.

There is a clear inconsistency in the reporting of levels of phosphates in food products (as well as in serum and urine), due largely to the form in which the results are expressed. Historically, phosphorus content has been expressed in terms of mg P_2O_5/100 g, which is usually applied to determination of total phosphorus and phytic acid in fertilisers, which allows for normalisation of P content across a range of products comprising different mixtures of phosphates. It is also applied to some foods and animal feeds. Other (particularly clinical) studies report phosphorus levels as mg P/kg. Modern analytical methods tend to report P content as mg/kg total phosphate or where possible as mg/kg individual ortho-, pyro- or polyphosphates.

In order to fulfil the requirements of EU regulation EU 1333/2008 with regard to the presence and maximum levels of phosphates, it is recommended that analytical results are expressed as either total phosphates ($P_3O_4^{3-}$ irrespective of counter ion), or in terms of the individual phosphate species, as mg/kg.

Literature sources show that spectrophotometry has been established as a reliable technique for the determination of total phosphate in foodstuffs. Similarly, IC has been applied successfully to a limited range of foodstuffs for the simultaneous determination of different phosphate additive species. The Panel noted the need for development of analytical methods since those currently available for total phosphate and phosphate speciation do not cover the entire range of foodstuffs permitted to contain phosphate additives.

3.1.6. Stability of the substance and fate in food

No information was identified in the literature on the reaction and fate of phosphoric acid or its calcium and magnesium salts in food. Phosphoric acid is soluble in water and is expected to dissociate in beverages and fresh food to phosphate and H^+ ions. No information was identified in the literature on the reaction and fate of sodium and potassium phosphates in food. Since sodium and potassium phosphates are freely soluble in water they are expected to be dissolved in beverages and fresh food to phosphate and the respective cations.

Phosphoric acid and its sodium and potassium salts dissociate readily after being added to foods and beverages, thereby affecting its technological function as an acidity regulator (Documentation provided to EFSA n. 8), whereas calcium and magnesium phosphates require solubilisation under acidic conditions (Documentation provided to EFSA n. 9,10).

The effects of phosphates in general on the colour and quality of salted fish are summarised by Þórarinsdóttir et al. (2010). Yellowing of the fish due to oxidation reduces the commercial quality. Positive effects of phosphates on colour and the commercial quality of the fish (by maintaining the natural colour of the fish) are thought to be due to reduced oxidation, which is brought about by the sequestering action of the phosphates on metals present in the salt used.

The addition of sodium phosphates to meat has been shown to have antioxidant effects that decrease the rate of oxidation of lipids in meat (Miller, 2010). Di-, tri- and higher phosphates are susceptible to the action of phosphatase enzymes, in particular during extraction from food or biological samples when they can be converted into monophosphates. Das et al. (2011) used Zn(II) and Cd(II)-based complexes to bind with tetrasodium diphosphate in order to investigate the activity

of alkaline phosphatase in physiological conditions. Allen and Cornforth (2009) describe the iron-binding activity of sodium tripolyphosphate in a lipid-free model system. At concentrations of 1 and 0.05 mg/mL, 88% and 21%, respectively, of the added iron was bound. This activity was considered to be the basis for the antioxidant effect of sodium tripolyphosphate. Weilmeier and Regenstein (2004) added sodium polyphosphate to mackerel samples and observed an antioxidant effect, although this was not as strong as the effect with propyl gallate, ascorbic acid or erythorbic acid. Jin et al. (2011) purified and characterised the tripolyphosphatase responsible for the hydrolysis of tripolyphosphates in rabbit psoas major muscle tissue.

Polyphosphates

All polyphosphates (also referred to as condensed phosphates) are subject to hydrolytic decomposition (reversion) when in solution. The rate of decomposition is affected by:

- Temperature
- pH (generally < 7 or > 11)
- Multivalent metal ions, e.g. Ca^{2+}, Fe^{2+}
- Concentration at mg/L level, since as the concentration increases, the reversion rate decreases
- Phosphatase enzymes
- Phosphate species.

It is generally accepted that pyrophosphate is the most stable, followed by tripolyphosphates. During hydrolysis of the longer chain phosphates, shorter chains as well as orthophosphates are formed. Among the shorter chains formed are pyrophosphates. Research suggests that when the pyrophosphate concentration increases, due to hydrolysis of higher polyphosphates, the rates of reversion diminish. It may be that an equilibrium is established between the higher condensed phosphates and their hydrolysis products.

Scharpf and Kichline (1967) showed that following the addition of long-chain sodium polyphosphate to cheese extracts in which the natural alkaline phosphatase activity was high, the concentration and distribution of phosphate species remained unchanged after storage at 3–7°C for 4 weeks. After 4 weeks storage at 20°C, the concentration of the long-chain species decreased from 89% to 64%, whereas the concentration of the orthophosphate species increased from 4% to 27%.

In a conservative review of polyphosphate breakdown and stability (Campden, 2012) it was reported that:

- Most polyphosphates added to food are broken down to orthophosphate units in the stomach and may be significantly hydrolysed to orthophosphates during storage and cooking.
- After 2 weeks of frozen storage, only 12% of the total phosphorus in uncooked shrimp muscle corresponded to the tripolyphosphate added. After ten weeks, the phosphorus levels corresponded to 45% orthophosphate. This was considered to be due to natural rather than heat-induced hydrolysis.
- At elevated temperatures, such as in steam cooking, sodium tripolyphosphate will hydrolyse rapidly to orthophosphates.
- Samples of three different commercially available cooked shrimp products treated with tripolyphosphate and stored frozen for 11 months, showed that the total polyphosphate was 87%, 89% and 103% of the original levels, indicating that very little hydrolysis occurred.

The stability of polyphosphates in fish and shrimps under various treatment and storage regimen was reported by Campden (2012). Samples were either untreated or treated and analysed after 0, 1, 2 and 3 days storage. The relative level of polyphosphate (expressed as P_2O_5) in raw shrimps was reduced from 1,500 mg/kg to 0 mg/kg after 4 days due to phosphatase activity. Conversely, no polyphosphate degradation was observed in cooked shrimp treated with polyphosphate (at 2,600 mg/kg) after cooking, indicating heat-induced phosphatase deactivation during cooking.

The addition of sodium phosphates to meat has been shown to have antioxidant effects that decrease the rate of oxidation of lipids in meat (Miller, 2010). Di-, tri- and higher phosphates are susceptible to the action of phosphatase enzymes, in particular during extraction from food or biological samples when they can be converted into monophosphates. Campden (2012) report that flash heat treatment with a microwave oven can be used to avoid this.

The impact of high temperature treatments of on the composition of polyphosphates with regard to phosphate chain length in aqueous solutions in the presence and absence of calcium ions has been reported by Rulliere et al. (2012). Treatment at 120°C for 10 min led to the hydrolytic degradation of

long-chain polyphosphates into orthophosphate and trimetaphosphate, whereas heating the salts to 100°C in aqueous solutions had little effect on composition. The presence of calcium ions increased the rate of hydrolysis of long-chain phosphates leading to increased amounts of trimetaphosphate and pyrophosphate end products. The evolution of emulsifying salts composition under heat treatment was reported to lead to modification of their chelating properties since short-chain phosphates are less efficient at chelating calcium than long-chain phosphates.

3.2. Authorised uses and use levels

Maximum levels of phosphates (E 338–341, E 343, E 450–452) have been defined in Annex II to Regulation (EC) No 1333/2008[13] on food additives, as amended. In this document, these levels are named maximum permitted levels (MPLs).

Currently, phosphates (E 338–341, E 343, E 450–452) are authorised food additives in the EU with MPLs ranging from 500 to 20,000 mg/kg expressed as P_2O_5 in 104 authorised uses and at *quantum satis* (QS) in four. The 108 different uses and use levels are corresponding to 65 different food categories. Table for converting phosphates into P_2O_5 and P is in Appendix B.

Table 2 summarises the food categories with their restrictions/exceptions that are permitted to contain added phosphates (E 338–341, E 343, E 450–452) and the corresponding MPLs as set by Annex II to Regulation (EC) No 1333/2008.

[13] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008, p. 16.

Table 2: MPLs of phosphates (E 338–341, E 343, E 450–452) in foods according to the Annex II to Regulation (EC) No 1333/2008

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
0	Food additives permitted in all categories of foods	Only foods in dried powdered form (i.e. foods dried during the production process, and mixtures thereof), excluding foods listed in table 1 of Part A of this Annex	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	10,000	(1),(4),(57)
01.1	Unflavoured pasteurised and sterilised (including UHT) milk	Only sterilised and UHT milk	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
01.4	Flavoured fermented milk products including heat-treated products		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	3,000	(1),(4)
01.5	Dehydrated milk as defined by Directive 2001/114/EC	Only partly dehydrated milk with less than 28% solids	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
01.5	Dehydrated milk as defined by Directive 2001/114/EC	Only partly dehydrated milk with more than 28% solids	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,500	(1),(4)
01.5	Dehydrated milk as defined by Directive 2001/114/EC	Only dried milk and dried skimmed milk	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,500	(1),(4)
01.6.3	Other creams	Only sterilised, pasteurised, UHT cream and whipped cream	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
01.7.1	Unripened cheese excluding products falling in category 16	Except mozzarella	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
01.7.5	Processed cheese		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
01.7.6	Cheese products (excluding products falling in category 16)	Only unripened products	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
01.8	Dairy analogues, including beverage whiteners	Only whipped cream analogues	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
01.8	Dairy analogues, including beverage whiteners	Only processed cheese analogues	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
01.8	Dairy analogues, including beverage whiteners	Only beverage whiteners	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	30,000	(1),(4)
01.8	Dairy analogues, including beverage whiteners	Only beverage whiteners for vending machines	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	50,000	(1),(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
02.2.1	Butter and concentrated butter and butter oil and anhydrous milkfat	Only soured cream butter	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
02.2.2	Other fat and oil emulsions including spreads as defined by Council Regulation (EC) No 1234/2007 and liquid emulsions	Only spreadable fats	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
02.3	Vegetable oil pan spray	Only water-based emulsion sprays for coating baking tins	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	30,000	(1),(4)
03	Edible ices		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
04.2.4.1	Fruit and vegetable preparations excluding compote	Only fruit preparations	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	800	(1),(4)
04.2.4.1	Fruit and vegetable preparations excluding compote	Only seaweed based fish roe analogues	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
04.2.4.1	Fruit and vegetable preparations excluding compote	Only glazings for vegetable products	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	4,000	(1),(4)
04.2.5.4	Nut butters and nut spreads	Only spreadable fats excluding butter	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
04.2.6	Processed potato products	Including prefried frozen en deep frozen potatoes	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
05.2	Other confectionery including breath refreshening microsweets	Only candied fruit	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	800	(1),(4)
05.2	Other confectionery including breath refreshening microsweets	Only sugar confectionery, except candied fruit	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
05.3	Chewing gum		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	*Quantum satis*	(1),(4)
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4	Only toppings (syrups for pancakes, flavoured syrups for milkshakes and ice cream; similar products)	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	3,000	(1),(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
05.4	Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
06.2.1	Flours		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,500	(1),(4)
06.2.1	Flours	Only self-raising flour	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
06.2.1	Flours	Only self-raising flour	E 450(ix)	Magnesium dihydrogen diphosphate	15,000	(4),(81)
06.3	Breakfast cereals		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
06.5	Noodles		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
06.5	Noodles		E 450(ix)	Magnesium dihydrogen diphosphate	2,000	(4),(81)
06.6	Batters		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	12,000	(1),(4)
06.6	Batters		E 450(ix)	Magnesium dihydrogen diphosphate	12,000	(4),(81)
07.1	Bread and rolls	Only soda bread	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
07.1	Bread and rolls	Only refrigerated, prepacked yeast based doughs used as basis for pizzas, quiches, tarts and similar products	E 450	Diphosphates	12,000	(4)
07.1	Bread and rolls	Only pizza dough (frozen or chilled) and 'tortilla'	E 450(ix)	Magnesium dihydrogen diphosphate	15,000	(4),(81)
07.2	Fine bakery wares		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
07.2	Fine bakery wares		E 450(ix)	Magnesium dihydrogen diphosphate	15,000	(4),(81)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
08.2	Meat preparations as defined by Regulation (EC) No 853/2004	Only *breakfast sausages*: in this product, the meat is minced in such a way so that the muscle and fat tissue are completely dispersed, so that fibre makes an emulsion with the fat, giving the product its typical appearance; Finnish grey-salted Christmas ham, *burger meat* with a minimum vegetable and/or cereal content of 4% mixed within the meat, *Kasseler, Bräte, Surfleisch, toorvorst, šašlõkk, ahjupraad, Bílá klobása, Vinná klobása, Sváteční klobása, Syrová klobása* and frozen vertical rotating meat spits made of sheep, lamb, veal and/or beef treated with liquid seasoning or from poultry meat treated with or without liquid seasoning used alone and/or combined as well as sliced and/or minced and designed to be roasted by a food business operator and then consumed by the final consumer	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
08.3.1	Non-heat-treated meat products		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
08.3.2	Heat–treated meat products	Except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben*	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
08.3.3	Casings and coatings and decorations for meat	Only glazings for meat	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	4,000	(1),(4)
09.1.1	Unprocessed fish	Only frozen and deep-frozen fish fillets	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
09.1.2	Unprocessed molluscs and crustaceans	Only frozen and deep-frozen molluscs and crustaceans	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
09.2	Processed fish and fishery products including molluscs and crustaceans	Only canned crustaceans products; surimi and similar products	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
09.2	Processed fish and fishery products including molluscs and crustaceans	Only fish and crustacean paste and in processed frozen and deep-frozen molluscs and crustaceans	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
09.2	Processed fish and fishery products including molluscs and crustaceans	Only salted fish of the Gadidae family that have been pre-salted by injecting and/or brine salting with an at least 18% salt solution and often followed by dry salting	E 450	Diphosphates	5,000	(1),(79)
09.2	Processed fish and fishery products including molluscs and crustaceans	Only salted fish of the Gadidae family that have been pre-salted by injecting and/or brine salting with an at least 18% salt solution and often followed by dry salting	E 451	Triphosphates	5,000	(1),(79)
09.2	Processed fish and fishery products including molluscs and crustaceans	Only salted fish of the Gadidae family that have been pre-salted by injecting and/or brine salting with an at least 18% salt solution and often followed by dry salting	E 452	Polyphosphates	5,000	(1),(79)
10.2	Processed eggs and egg products	Only liquid egg (white, yolk or whole egg)	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	10,000	(1),(4)
11.1	Sugars and syrups as defined by Directive 2001/111/EC	Only dried powdered foods	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	10,000	(4)
11.4.2	Table-top sweeteners in powder form		E 341	Calcium phosphates	*Quantum satis*	
12.1.1	Salt		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	10,000	(1),(4)
12.1.2	Salt substitutes		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	10,000	(1),(4)
12.5	Soups and broths		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	3,000	(1),(4)
12.6	Sauces		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
12.9	Protein products, excluding products covered in category 1.8	Only vegetable protein drinks	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)
13.1.1	Infant formulae as defined by Directive 2006/141/EC		E 338	Phosphoric acid	1,000*	(4),(44)
13.1.1	Infant formulae as defined by Directive 2006/141/EC		E 339	Sodium phosphates	1,000*	(4),(15)
13.1.1	Infant formulae as defined by Directive 2006/141/EC		E 340	Potassium phosphates		(4),(15)
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC		E 338	Phosphoric acid		(4),(44)
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC		E 339	Sodium phosphates	1,000*	(4),(15)
13.1.2	Follow-on formulae as defined by Directive 2006/141/EC		E 340	Potassium phosphates		(4),(15)
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only processed cereal based foods and baby foods, only for pH adjustment	E 338	Phosphoric acid	1,000*	(4)
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only cereals	E 339	Sodium phosphates	1,000*	(4),(20)
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only cereals	E 340	Potassium phosphates	1,000*	(4),(20)
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only cereals	E 341	Calcium phosphates	1,000*	(4),(20)
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only in fruit-based desserts	E 341	Calcium phosphates	1,000*	(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
13.1.3	Processed cereal-based foods and baby foods for infants and young children as defined by Directive 2006/125/EC	Only biscuits and rusks	E 450	Diphosphates	5,000*	(4),(42)
13.1.4	Other foods for young children		E 338	Phosphoric acid		(1),(4),(44)
13.1.4	Other foods for young children		E 339	Sodium phosphates	1,000*	(1),(4),(15)
13.1.4	Other foods for young children		E 340	Potassium phosphates	1,000*	(1),(4),(15)
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants	Only for pH adjustment	E 338	Phosphoric acid	1,000*	(1),(4)
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants		E 339	Sodium phosphates	1,000*	(1),(4),(20)
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants		E 340	Potassium phosphates	1,000*	(1),(4),(20)
13.1.5.1	Dietary foods for infants for special medical purposes and special formulae for infants		E 341	Calcium phosphates	1,000*	(1),(4),(20)
13.1.5.2	Dietary foods for babies and young children for special medical purposed as defined in Directive 1999/21/EC		E 338	Phosphoric acid	1,000*	(4),(44)
13.1.5.2	Dietary foods for babies and young children for special medical purposed as defined in Directive 1999/21/EC		E 339	Sodium phosphates	1,000*	(4),(15)
13.1.5.2	Dietary foods for babies and young children for special medical purposed as defined in Directive 1999/21/EC		E 340	Potassium phosphates	1,000*	(4),(15)
13.1.5.2	Dietary foods for babies and young children for special medical purposed as defined in Directive 1999/21/EC		E 341	Calcium phosphates	1,000*	(4),(20)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
13.1.5.2	Dietary foods for babies and young children for special medical purposed as defined in Directive 1999/21/EC	Only biscuits and rusks	E 450	Diphosphates	5,000*	(4),(42)
13.2	Dietary foods for special medical purposes defined in Directive 1999/21/EC (excluding products from food category 13.1.5)		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
13.3	Dietary foods for weight control diets intended to replace total daily food intake or an individual meal (the whole or part of the total daily diet)		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
13.4	Foods suitable for people intolerant to gluten as defined by Regulation (EC) No 41/2009		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
14.1.1	Water, including natural mineral water as defined in Directive 2009/54/EC and spring water and all other bottled or packed waters	Only prepared table waters	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	500	(1),(4)
14.1.4	Flavoured drinks		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	700	(1),(4)
14.1.4	Flavoured drinks	Only sport drinks	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	500	(1),(4)
14.1.4	Flavoured drinks	Only chocolate and malt dairy-based drinks	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
14.1.4	Flavoured drinks	Only whey protein containing sport drinks	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	4,000	(1),(4)
14.1.4	Flavoured drinks	Only vegetable protein drinks	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	20,000	(1),(4)

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
14.1.5.2	Other	Only coffee-based drinks for vending machines; Instant tea and instant herbal infusions	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	2,000	(1),(4)
14.2.3	Cider and perry		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.4	Fruit wine and made wine		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.5	Mead		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Except: whisky, whiskey	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.7.1	Aromatised wines		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.7.2	Aromatised wine-based drinks		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.7.3	Aromatised wine-product cocktails		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
14.2.8	Other alcoholic drinks including mixtures of alcoholic drinks with non-alcoholic drinks and spirits with less than 15% of alcohol		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	1,000	(1),(4)
15.1	Potato-, cereal-, flour- or starch-based snacks		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
15.2	Processed nuts		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)
16	Desserts excluding products covered in category 1, 3 and 4		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	3,000	(1),(4)
16	Desserts excluding products covered in category 1, 3 and 4	Only dry powdered dessert mixes	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	7,000	(1),(4)
17.1	Food supplements supplied in a solid form, excluding food supplements for infants and young children		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	*Quantum satis*	

Food category code	Food category name	Restrictions/exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008
17.2	Food supplements supplied in a liquid form, excluding food supplements for infants and young children		E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	*Quantum satis*	

MPL: maximum permitted level; UHT: Ultra High Temperature.
(1): The additives may be added individually or in combination.
(4): The maximum level is expressed as P_2O_5.
(15): E 339 and E 340 are authorised individually or in combination and in conformity with the limits set in Directives 2006/141/EC, 2006/125/EC, 1999/21/EC.
(20): E 339, E 340 and E 341 are authorised individually or in combination.
(44): In conformity with the limits set in Directives 2006/141/EC, 2006/125/EC, 1999/21/EC.
(57): The maximum level shall apply unless a different maximum level is specified in points 01 to 18 of this Annex in relation to individual foods or categories of foods.
(79): The maximum level applies to the sum of E 450, E 451 and E 452 used individually or in a combination.
(81): The total amount of phosphates shall not exceed the maximum level for E 338–452.
*: The maximum levels of use indicated refer to foods ready for consumption prepared following manufacturer's' instructions, for all subcategories under 13.1 Foods for infants and young children.

The Panel noted that for three food categories, no number for the maximum level is provided for certain provisions (see above for FC 13.1.1 for food additive E 340, FC 13.1.2 for food additive E 338 and E 340 and for FC 13.1.4 for food additive E 338). However, the footnotes associated with the provisions refer to the limits set in Directives 2006/141/EC, 2006/125/EC and 1999/21/EC which shall be respected. In addition, for E 340 in FC 13.1.1 and 13.1.2 the use level is set up individually or in combination with E 339 by the footnote (15).

The directives considered in the footnotes (15) or (44) prescribe that the maximum level of 1,000 mg/kg in the FC 13.1.1 for instance are applicable to all the phosphates additives authorised in the same food category. In the MPL scenario, the Panel agreed to use a MPL of 1,000 mg/kg for the food categories that for which MPLs were not provided (FCs 13.1.1, 13.1.2 and 13.1.4).

According to Annex III, Part 1 of Regulation (EC) No 1333/2008, calcium phosphates (E 341) is authorised as a carrier in all food additives at QS.

According to Annex III, Part 2 of Regulation (EC) No 1333/2008, E 338, E 339, E 340, E 343, E 450, E 451 are also authorised as food additive in preparations of the colour E 163 anthocyanins with a maximum level in the preparations of 40,000 mg/kg singly or in combination (expressed as P_2O_5). E 341 is also authorised, according to Part 2, as food additive:

- in colour and emulsifier preparations with a maximum level in the preparations of 40,000 mg/kg (expressed as P_2O_5);
- in polyol preparations and E 412 guar gum preparations with a maximum level in the preparation of 10,000 mg/kg (expressed as P_2O_5).

According to Annex III, Part 3 of Regulation (EC) No 1333/2008, phosphoric acid (E 338) is also authorised as a food additive in food enzymes with a maximum level in the enzymes preparation of 10,000 mg/kg (expressed as P_2O_5) and at QS in the final products (food or beverages).

According to Annex III, Part 3 of Regulation (EC) No 1333/2008, E 339, E 340, E 341, E 343 are also authorised as a food additive in food enzymes with a maximum level in the enzymes preparation of 50,000 mg/kg (expressed as P_2O_5) and at QS in the final products (food or beverages). These food additives are also authorised to be used as carriers.

According to Annex III, Part 3 of Regulation (EC) No 1333/2008, E 450, E 451, E 452 are also authorised as a food additive in food enzymes with a maximum level in the enzymes preparation of 50,000 mg/kg (expressed as P_2O_5) and at QS in the final products (food or beverages).These food additives are not authorised to be used as carriers.

According to Annex III, Part 4, phosphates (E 338–341, E 343, E 450–452) are authorised at the maximum level of 40,000 mg/kg (singly or in combination expressed as P_2O_5) in all flavourings.

In addition, according to Annex III, Part 5, Section A of Regulation (EC) No 1333/2008, phosphates (E 338–341, E 343, E 450–452) are also authorised at the maximum level of 40,000 mg/kg expressed as P_2O_5 in the nutrient preparation, in all nutrients.

According to Annex III, Part 5, Section B of Regulation (EC) No 1333/2008, tricalcium phosphate (E 341(iii) is also authorised at the maximum carry-over of 150 mg/kg as P_2O_5 and within the limit for calcium, phosphorus and calcium:phosphorus ratio as set in Directive 2006/141/EC in all nutrients in infant formulae and follow-on formulae as defined by Directive 2006/141/EC; and at the maximum level of 1,000 mg/kg expressed as P_2O_5 from all uses in final food mentioned in point 13.1.3 of Part E of Annex II is respected in all nutrients in processed cereal based foods and baby foods for infants and young children as defined by Directive 2006/141/EC.

3.2.1. Proposed extension of use

One request for extension of use was also considered in the exposure estimates. The request referred to the removal of the restriction 'only sugar confectionary' in the food category 05.2 'Other confectionary including breath refreshing microsweets'. This request would change the Regulation (EC) No 1333/2008 as reported in Table 3.

Table 3: Proposed uses and maximum use levels for phosphates (E 338–341, E 343, E 450–452) in food category 05.2 following the requested extension of use

Food category code	Food category name	Restrictions/ exceptions	E-number	Name	MPL (mg/L or mg/kg as appropriate)	Footnotes (as in Reg (EC) No 1333/2008)
05.2	Other confectionery including breath refreshening microsweets	Only candied fruit	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	800	(1),(4)
05.2	Other confectionery including breath refreshening microsweets	Except candied fruit	E 338–452	Phosphoric acid–phosphates – di-, tri- and polyphosphates	5,000	(1),(4)

MPL: maximum permitted level.
(1): The additives may be added individually or in combination.
(4): The maximum level is expressed as P_2O_5.

3.3. Exposure data

3.3.1. Reported use levels or data on analytical levels of phosphates (E 338–341, E 343, E 450–452)

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to QS. In the case of phosphates additives, only chewing-gum and food supplements were authorised at QS.

In the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 regarding the re-evaluation of approved food additives, EFSA issued a public call[14] for occurrence data (usage level and/or concentration data) on phosphates (E 338–341, E 343, E 450–452). In response to this call, both types of data on phosphates (E 338–341, E 343, E 450–452) were submitted to EFSA by industry and Member States, respectively.

Summarised data on reported use levels in foods provided by industry

Industry provided EFSA with data on use levels (n = 1,298) of phosphates (E 338–341, E 343, E 450–452) in foods for 89 out of the 108 authorised uses in which phosphates (E 338–341, E 343, E 450–452) are authorised.

Updated information on the actual use levels of phosphates (E 338–341, E 343, E 450–452) in foods was made available to EFSA by the Association des Entreprises Produits Alimentaires Elabores (ADEPALE), Association of the European Self-Medication Industry (AESGP), Comité Européen des Fabricants de Sucre (CEFS), Dr Loges Naturheilkunde neu entdecken, European Chemical Industry Council (CEFIC), European Dairy Association (EDA), European Fish Processors and Traders Association & European Federation of National Organisations of Importers and Exporters of Fish (AIPCE-CEP), European Potato Processors' Association (EUPPA), Food Drink Europe (FDE), Food Supplement Europe (FSE), IMACE, International Chewing Gum Association (ICGA), Intersnack, L'ALLIANCE 7, Nathura, Specialised Nutrition Europe (SNE).

The Panel noted that a data provider (namely CEFIC) is not a food industry using phosphates in its food products but is an association representing food additive producers/chemical suppliers and not directly using these substances as additives in foods. Usage levels reported by food additive producers are not considered at the same level as those provided by food industry. Food additive producers may recommend usage levels to the food industry but the final levels might, ultimately, be different. Therefore, unless food additive producers confirm that the recommended levels are used by food industry, they are not considered in the refined exposure scenario. In this opinion, data coming from CEFIC were not considered in the refined assessment. These data are nevertheless presented in the Appendix F.

Data provided by Nathura (n = 3) were also discarded from the current exposure estimates. These data were initially checked with the provider but the levels submitted were found not to be correct as these levels would results in a phosphates content which is higher than 100%.

The Panel noted that 325 usage levels referred to niche products. When other usage levels were available for the same authorised uses, the Panel decided to exclude them from further analysis. Levels from niche products were used for unflavoured pasteurised and sterilised (including UHT) milk (FC 01.1), chewing-gum (FC 05.3) and processed cereal-based foods and baby foods for infants and young children (FC 13.1.3) in the absence of other levels.

The Panel also noted that levels provided for the use of phosphates as nutrient sources (e.g. phosphates in formulae) and not as food additives. These levels were not taken into account for estimating exposure of phosphates (E 338–341, E 343, E 450–452) as food additives.

Some data (n = 190) were provided as phosphates ('E 338–452') or as mixture of different E-numbers.

Most of the data submitted to EFSA were expressed directly in P_2O_5, the other in the food additive added. In the latter, thanks to the availability of the specific E-number, the use levels were converted into P_2O_5, based on the conversion factors (see Appendix B). However, some data providers are using phosphates in a subcomponent of their final product. In these instances, the E number subcategories (i, ii, iii) were not specified. Thus, the levels could not be expressed as P_2O_5, which is the case for all data on snacks (n = 7) and 73 levels on food supplements. Food supplements and snacks use levels not

[14] http://www.efsa.europa.eu/sites/default/files/consultation/170223.pdf

expressed as P_2O_5, were converted using the converting factors reported in Appendix B. In case the salt is not specified, the factor used to convert this level in P_2O_5 is the one of the anhydrous form and this could lead to an overestimation. The use levels not expressed as P_2O_5 are indicated in Appendix F.

Some levels were submitted for food categories not listed in Table 1. However, phosphates could be used in those as these foods are in dried powdered form and can contain phosphates. This is the case for:

- icing sugar (belonging to FC 11.2)
- pasta (FC 06.4.2) with seasonings.

Some levels were also submitted for FC 07.1 Bread and rolls. Foods belonging to this category can contain phosphates from their authorisation and uses in their ingredients [e.g. flour (FC 06.2.1), decorations, coatings and fillings (FC 05.4)]. After considering all the data, the Panel agreed that for FC 07.1 maximum uses reported by industry were used in the regulatory maximum exposure assessment scenario.

Appendix F provides data on the use levels of phosphates (E 338–341, E 343, E 450–452) in foods as reported by industry.

Summarised data on analytical results in food submitted by Member States

In total, 2,418 analytical results were reported to EFSA by 10 countries: Belgium (n = 379), the Czech Republic (n = 674), Germany (n = 310), Hungary (n = 302), Ireland (n = 42), Italy (n = 18), Lithuania (n = 66), Portugal (n = 6), Spain (n = 325) and the UK (n = 296). Substances analysed were expressed either as phosphorus (P), phosphoric acid or sum of phosphates expressed as P_2O_5. For this evaluation all results were converted to P.

Some of the analytical results were left-censored (LC): either not quantified (< LOQ) in 824 samples or not detected (< LOD) in 14 samples. To consider left-censored analytical data (i.e. analytical results < LOD or < LOQ), the substitution method as recommended in the 'Principles and Methods for the Risk Assessment of Chemicals in Food' (WHO, 2009) and the EFSA scientific report 'Management of left-censored data in dietary exposure assessment of chemical substances' (EFSA, 2010) was used. In the present opinion, analytical data below LOD or LOQ were assigned half of LOD or LOQ, respectively. Therefore, it should be noted that the use of middle-bound (MB) LOD/LOQ values (half of LOD or LOQ) in the exposure assessment, may have resulted in either an overestimation, where phosphates were not present, or underestimation, where the concentration was between the MB and LOQ/LOD value, but the analytical method was not able to detect or quantify it. The higher percentage of left-censored data was observed for the food categories confectionary (FC 05.2, 96.7% of LC data), water (FC 14.1.1, 81.8% LC data), flavoured drinks (FC 14.1.4, 72.6% of LC data). Some left-censored samples were identified with a very high LOQ. While checking LOQ with the data provider, it appears that there was an error in the reporting of the LOQ. Therefore, these samples were discarded.

Complete information on the methods of analysis (e.g. validation) was not made available to EFSA, but all samples were analysed by accredited laboratories. Data were sampled between 2009 and 2016 and analysed between 2009 and 2017. The Panel noted that the methods of analysis applied are generally not able to differentiate between phosphates added as food additives and naturally present in foods.

The majority of the data (n = 2,252) were expressed as μg/kg and were converted to mg/kg as were levels expressed in percent (n = 66) whereas the levels expressed in kcal (n = 1) or per 100 kcal (n = 99) were discarded since no information on the food energy content was available.

The food categories with the most data were FC 15.1 snacks (n = 507), FC 14.1.4 flavoured drinks (n = 500), confectionery FC 05.2 (n = 212), unprocessed fruits and vegetables FC 04.1 (n = 159).

Almost all food categories according to the food additives nomenclature (Part D to Regulation No 1333/2008) are covered by the analytical data available. Data on chewing-gums, processed eggs, some sugars and syrups, salts, FSMP for infants and young children, some alcoholic beverages and food supplements were not available.

Overall, 2,271 analytical results reported for phosphates in foods were used by the Panel in the exposure assessment.

Appendix G shows the analytical results of phosphates in foods as reported by Member States.

3.3.2. Summarised data extracted from the Mintel's Global New Products Database

The Mintel's GNPD is an online database which monitors new introductions of packaged goods in the market worldwide. It contains information of more than 1,000,000 food and beverage products

that are or have been available on the European food market. Mintel started covering EU's food markets in 1996, currently having 20 out of its 28 member countries and Norway presented in the Mintel's GNPD.[15]

For the purpose of this Scientific Opinion, the Mintel's GNPD[16] was used for checking the labelling of food and beverages products and food supplements for phosphates (E 338–341, E 343, E 450–452) within the EU's food market as the database contains the compulsory ingredient information on the label.

According to the Mintel's GNPD, phosphates (E 338–341, E 343, E 450–452) was labelled on many products (n = 44178) between January 2014 and March 2019 (more than 84,000 since 1996).

Appendix H lists the percentage of the food products labelled with phosphates (E 338–341, E 343, E 450–452) out of the total number of food products per food subcategories according to the Mintel's GNPD food classification. The percentages ranged from less than 0.1% in many food subcategories to 73% for evaporated milk (up to 100% in the Mintel's GNPD food subcategory 'Growing Up Milk (4+ years)' but this category contains only 3 products). Infants and toddlers formulae contain quite largely phosphates in their ingredients (more than 50% of products). Bread and bread products as well as fine bakery wares are also labelled with phosphates for more than 10% of the products on the European market.

The average percentage of foods labelled to contain phosphates (E 338–341, E 343, E 450–452) was 9.6%.

No data were provided to EFSA for certain products labelled as containing phosphates in which phosphates are authorised. These include:

- alcoholic beverages,
- white milk: the few milks found in Mintel are mainly enriched with calcium, or white milk other than from cow, e.g. goat, sheep. Levels of phosphates were provided for goat milk only, while phosphates (E 338–341, E 343, E 450–452) are authorised in all sterilised and UHT milk.
- eggs & egg products,
- nuts,
- hard cheese & semi-hard cheese: it is not clear whether these food items are part of FC 01.7.5 Processed cheeses or contain phosphates because are seasoned cheeses or cheese with other ingredients (such as chorizo),
- vegetables.

Phosphates (E 338–341, E 343, E 450–452) were found to be labelled in Mintel food categories of nectar and juices. FCs 14.1.2 and 14.1.3 are not authorised to contain phosphates. However, it is not clear whether nectars and juices as coded in the Mintel GNPD completely match with fruit juices and fruit nectars as defined in the legislation.

In most of these subcategories, the percentage of foods labelled with phosphates was low.

Approximately one-third of the products are labelled as containing diphosphates (E 450).

3.3.3. Food consumption data used for exposure assessment

EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a). Consumption surveys added in the Comprehensive database in 2015 were also taken into account in this assessment.[17]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible subjects' underreporting and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database includes the currently best available food consumption data across Europe.

[15] Missing Bulgaria, Cyprus, Estonia, Latvia, Lithuania, Luxembourg, Malta and Slovenia.
[16] http://www.gnpd.com/sinatra/home/ accessed on 18/3/2019.
[17] Available online: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Food consumption data from the following population groups were used for the exposure assessment: infants, toddlers, children, adolescents, adults and the elderly. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 4).

Table 4: Population groups considered for the exposure estimates of phosphates (E 338–341, E 343, E 450–452)

Population	Age range	Countries with food consumption surveys covering more than 1 day
Infants < 16 weeks	From birth up to and including 16 weeks of age	Not applicable(c)
Infants	From more than 12 weeks up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers(a)	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children(b)	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly(b)	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Netherlands, Sweden, UK

(a): The term 'toddlers' in the EFSA Comprehensive Database corresponds to 'young children' in Regulations (EC) No 1333/2008 and (EU) No 609/2013.
(b): The terms 'children' and 'the elderly' correspond, respectively, to 'other children' and the merge of 'elderly' and 'very elderly' in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011a).
(c): Recommended values of 200 and 260 mL/kg bw per day as conservative mean and high level consumption values were used (EFSA Scientific Committee, 2017).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011b). Nomenclature from the FoodEx classification system has been linked to the food categorisation system (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, the FoodEx food codes were matched to the FCS food categories.

Food categories considered for the exposure assessment of phosphates (E 338–341, E 343, E 450–452)

The food categories in which the use of phosphates (E 338–341, E 343, E 450–452) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system), at the most detailed level possible (up to FoodEx Level 4) (EFSA, 2011b).

Some food categories or their restrictions/exceptions are not referenced in the EFSA Comprehensive Database and could therefore not be taken into account in the present estimate. This was the case for 15 authorised uses (Appendix I) and may have resulted in an underestimation of the exposure. The authorised uses which were not taken into account are described below (in ascending order of the FCS codes):

- 01.7.6 Cheese products (excluding products falling in category 16), only unripened products
- 02.3 Vegetable oil pan spray, only water-based emulsion sprays for coating baking tins
- 04.2.4.1 Fruit and vegetable preparations excluding compote, only seaweed based fish roe analogues
- 04.2.4.1 Fruit and vegetable preparations excluding compote, only glazing for vegetable products
- 06.2.1 Flours, only self-raising flour. Self-raising flour is not a food item available in the FoodEx nomenclature and only flour (with no restrictions) was used at the MPL of 2,500 mg/kg.
- 06.6 Batters

- 07.1 Bread and rolls, only soda bread
- 08.2 Meat preparations as defined by Regulations (EC) No 853/2004, only *breakfast sausages*: in this product, the meat is minced in such a way so that the muscle and fat tissue are completely dispersed, so that fibre makes an emulsion with the fat, giving the product its typical appearance; Finnish grey salted Christmas ham, *burger meat* with a minimum vegetable and/or cereal content of 4% mixed within the meat, *Kasseler, Bräte, Surfleisch, toorvorst, šašlõkk, ahjupraad, Bílá klobása, Vinná klobása, Sváteční klobása, Syrová klobása* and frozen vertical rotating meat spits made of sheep, lamb, veal and/or beef treated with liquid seasoning or from poultry meat treated with or without liquid seasoning used alone and/or combined as well as sliced and/or minced and designed to be roasted by a food business operator and then consumed by the final consumer.
- 08.3.3 Casings and coatings and decorations for meat, only glazings for meat
- 10.2 Processed eggs and egg products, only liquid egg (white, yolk or whole egg)
- 12.1.2 Salt substitutes
- 14.1.1 Water, including natural mineral water as defined in Directive 2009/54/EC and spring water and all other bottled or packed waters, only prepared table waters
- 14.1.4 Flavoured drinks, the restriction *only whey protein containing sport drinks* cannot be differentiated from the sport drinks, therefore all sport drinks were taken into account at MPL of 500 mg/kg, while MPL for *whey protein containing sport drinks* equals 20,000 mg/kg.
- 14.2.4 Fruit wine and made wine
- 14.2.5 Mead

For the following authorised uses, the restrictions/exceptions which apply to the use of phosphates (E 338–341, E 343, E 450–452) could not be taken into account, and therefore, the whole food category was considered in the exposure assessment. This applies to seven food categories (Appendix I) and may have resulted in an overestimation of the exposure:

- 01.5 Dehydrated milk as defined by Directive 2001/114/EC, the two restrictions (only partly dehydrated milk with less than 28% solids/only partly dehydrated milk with more than 28% solids) cannot be differentiated. Foods from the FC 01.5 were divided into two subcategories: dehydrated milk at the MPL of 1,500 mg/kg and dried milk at the MPL of 2,500 mg/kg.
- 01.8 Dairy analogues, including beverage whiteners, only beverage whiteners for vending machines. All beverages whiteners (for vending machines or not) were taken into account at the same MPL of 30,000 mg/kg.
- 05.4 Decorations, coatings and fillings, except fruit based fillings covered by category 4.2.4, the restriction 'only toppings (syrups for pancakes, flavoured syrups for milkshakes and ice cream; similar products' cannot be differentiated from the whole food category. Therefore the whole FC 05.4 was taken into account at the MPL of 5,000 mg/kg.
- 08.3.2 Heat–treated meat products, except *foie gras, foie gras entier, blocs de foie gras, Libamáj, libamáj egészben, libamáj tömbben.*
- 09.2 Processed fish and fishery products including molluscs and crustaceans, only salted fish of the Gadidae family that have been pre-salted by injecting and/or brine salting with an at least 18% salt solution and often followed by dry salting: fishes from the Gadidae family (i.e. cod and whiting) were taken into account as the restriction cannot be applied.
- 14.1.5.2 Other, only coffee-based drinks for vending machines
- 16 Desserts, only dry powdered mixes.

The FCs 17.1/17.2 Food supplements, in solid, liquid form, the form cannot be differentiated and the same use level was applied to the whole FC 17. This would lead to an overestimate if use levels of food supplements supplied in solid form are higher than use levels of food supplements supplied in liquid form.

Phosphates (E 338–341, E 343, E 450–452) are authorised in the sterilised and UHT milk of the FC 01.1 unflavoured pasteurised and sterilised milk. Use levels were reported from food industry only on goat milk. Considering that information retrieved from Mintel shows few cow milks (mainly enriched ones), goat or sheet milk labelled with phosphates (E 338–341, E 343, E 450–452), only goat milk available in the FoodEx nomenclature were considered.

Phosphates (E 338–341, E 343, E 450–452) are also allowed in FC 13.2, 13.3 and 13.4. Food items under food categories 13.2, 13.3 and 13.4 consumed by population groups – children, adolescents, adults and the elderly – may be very diverse and, in addition, there is very limited information on their

consumption. Therefore, eating occasions belonging to the food categories 13.2, 13.3 and 13.4 were reclassified under food categories in accordance to their main component.

The use levels available for food categories 13.2, 13.3 and 13.4 were not considered for the exposure assessment.

3.4. Exposure estimates

3.4.1. Exposure to phosphates (E 338–341, E 343, E 450–452) from its use as food additives

The Panel estimated the chronic dietary exposure to phosphates (E 338–341, E 343, E 450–452) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Dietary exposure to phosphates (E 338–341, E 343, E 450–452) was calculated by multiplying concentrations of phosphates (E 338–341, E 343, E 450–452) expressed as P_2O_5 per food category (Appendix I) with their respective consumption amount per kilogram body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Dietary surveys with only 1 day per subject were excluded as they are considered as not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 4). On the basis of these distributions, the mean and 95th percentile of exposure were calculated per survey and per population group. The 95th percentile of exposure was only calculated for those population groups with a sufficiently large sample size (EFSA, 2011a). Therefore, in the present assessment, the 95th percentile of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not estimated.

Reported use levels from industry give information on the amount of the food additive added to food.

Exposure assessment to phosphates (E 338–341, E 343, E 450–452) was carried out by the FAF Panel based on two different sets of concentration data: (1) MPLs as set down in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*). These two scenarios are discussed in detail below.

These scenarios do not consider the consumption of food supplements and FSMP. These exposure sources are covered in two additional scenarios detailed below (*foods for special medical purposes consumer only scenario* and *food supplements consumers only scenario*).

A possible additional exposure from the use of phosphates (E 338–341, E 343, E 450–452) as food additives as carriers in food additives, in food colours, food enzymes, food flavourings and in nutrients in accordance with Annex III to Regulation (EC) No 1333/2008 (Parts 1, 2, 3, 4, 5 Sections A and B) was not considered in exposure assessment scenarios.

Regulatory maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008 and listed in Table 2. For the four uses authorised according to QS, the maximum of the reported use levels was used (Appendix I).

The Panel considers the exposure estimates derived following this scenario as the most conservative since it is assumed that that the population will be exposed to the food additives present in food at the MPL/maximum reported use levels over a lifetime.

Refined exposure assessment scenario

The refined exposure assessment scenario is based on use levels reported by food industry. This exposure scenario can consider only authorised uses for which these data were available to the Panel.

Appendix I summarises the concentration levels of phosphates (E 338–341, E 343, E 450–452) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on two model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to phosphates (E 338–341, E 343, E 450–452) present at the maximum reported use level for one food category. This exposure estimate is calculated as follows:

- Combining food consumption with the maximum of the reported use levels for the main contributing food category at the individual level.
- Using the mean of the typical reported use levels for the remaining authorised uses.

- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to phosphates (E 338–341, E 343, E 450–452) present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels for all authorised uses.

Exposure assessment for specific population groups

- Infants below 16 weeks:

Exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives for infants below 16 weeks was also estimated. This scenario is based on the recommended consumption levels from Scientific Committee Guidance (EFSA Scientific Committee, 2017). This guidance 'recommends values of 200 and 260 mL/kg bw per day as conservative mean and high level consumption values to be used for performing the risk assessments of substances which do not accumulate in the body present in food intended for infants below 16 weeks of age'. These recommended consumption levels correspond to 14- to 27-day-old infants consumption. For regulatory maximum level exposure assessment scenario, MPL for infant formulae of 1,000 mg/kg was used and for the refined scenario, reported use levels (typical and maximum) were considered.

Exposure on a body weight basis is the metric used to compare exposure with the ADI value but exposure per person is also provided in the Tables for ease of reference. A body weight of 4 kg (EFSA NDA Panel, 2018) was used for this specific assessment of infants below 16 weeks of age. This body weight is the median weight of 4 weeks girl infants according to the report from Van Buuren et al. (2012).

Some carers use bottled water rather than tap water to reconstitute formulae powder and make it ready to feed. Phosphates are permitted to be added to bottled waters (Table 2, food category 14.1.1) but only for 'prepared table waters'. Inspection of the Mintel database revealed no incidences of still (uncarbonated) bottled water containing phosphate additives being recorded. There were a few entries (n = 14) covered by this general food code but they were for flavoured water beverages. The scenario of using bottled water containing phosphate additives to reconstitute formulae power was therefore not used.

- 'Food supplement consumers only':

Phosphates (E 338–341, E 343, E 450–452) are authorised in the food category 17 Food supplements as defined in Directive 2002/46/EC excluding food supplements for infants and young children. As exposure via food supplements may deviate largely from the one via food, and that the number of food supplement consumers may be low depending on populations and surveys, an additional estimate was calculated in order to reflect additional exposure to food additives from food supplements compared to exposure to food additives excluding these sources. This will be estimated as follow:

- Consumers only of food supplements will be assumed to be exposed to phosphates (E 338–341, E 343, E 450–452) present at the maximum reported use levels on a daily basis via consumption of food supplements.
- For the remaining authorised uses, the mean of the typical reported use levels is used.

As food category 17 do not consider food supplements for infants and toddlers as defined in the legislation, exposure to phosphates (E 338–341, E 343, E 450–452) from food supplements are not estimated for these two population groups.

This exposure assessment included all authorised uses for general population and food supplements (Appendix I).

- FSMP consumers only:

As phosphates (E 338–341, E 343, E 450–452) are also authorised in the food categories 13.1.5.1 and 13.1.5.2, an additional exposure assessment taking into account these two food categories was performed to estimate the exposure of infants and toddlers who may eat and drink these FSMP.

The consumption of these foods is not reported in the EFSA Comprehensive database. To consider potential exposure to phosphates (E 338–341, E 343, E 450–452) via these foods, the Panel assumes that the amount consumed of FSMP in infants and toddlers resembles that of comparable foods in infants and toddlers from the general population. Thus, the consumption of FSMP categorised as food category 13.1.5 is assumed to equal that of formulae and food products categorised as food categories 13.1.1, 13.1.2, 13.1.3 and 13.1.4.

Phosphates (E 338–341, E 343, E 450–452) are also allowed in FSMP consumed in other population groups (FC 13.2, 13.3 and 13.4). Food items under food categories 13.2, 13.3 and 13.4 consumed by population groups – children, adolescents, adults and the elderly – may be very diverse and, in addition, there is very limited information on their consumption. Therefore, eating occasions belonging to the food categories 13.2, 13.3 and 13.4 were reclassified under food categories in accordance to their main component. The use levels available for food categories 13.2, 13.3 and 13.4 were not considered for the exposure assessment and no exposure estimates were calculated for these population groups.

This exposure assessment was estimated as follows:

- Consumers only of FSMP were assumed to be exposed to phosphates (E 338–341, E 343, E 450–452) present at the maximum reported use level on a daily basis via consumption of food categories 13.1.5.1 and 13.1.5.2 (infant formulae, follow-on formulas and processed cereal-based foods and baby foods for infants and young children as defined by Commission Directive 2006/125/EC).
- For the remaining authorised uses, the mean of the typical reported use levels was used.

This estimate included 50 authorised uses (Appendix I).

Dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives

Tables 5a,b summarise the estimated exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in seven population groups (Table 4) according to the different exposure scenarios. Results are presented in mg phosphorus (P) per person and per day and in mg P/kg bw per day. Results expressed mg P_2O_5 per person and per day and mg P_2O_5/kg bw per day are available in the appendixes to the opinion (Appendix J). Detailed results per population group and survey (in mg P_2O_5/kg bw per day) are also presented in Appendix K.

Table 5a: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in the regulatory maximum level exposure assessment scenario and in the refined exposure assessment scenarios, in seven population groups (minimum –maximum across the dietary surveys in **mg P/person per day**)

	Infants below 16 weeks	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario							
• Mean	349	198–998	446–1,554	725–1,751	857–1,945	850–1,867	890–1,848
• 95th percentile	454	419–1,714	753–2,052	1,070–2,959	1,461–3,462	1,530–3,638	1,510–3,551
Refined estimated exposure assessment scenario							
Brand-loyal scenario							
• Mean	213	96–309	101–372	108–620	130–733	319–722	337–747
• 95th percentile	278	222–570	203–745	215–1,291	287–1,603	658–1,600	683–1,559
Non-brand-loyal scenario							
• Mean	192	81–141	78–152	69–237	74–298	126–278	121–241
• 95th percentile	250	191–253	153–266	135–613	155–749	253–636	212–480

Table 5b: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in the regulatory maximum level exposure assessment scenario and in the refined exposure assessment scenarios, in seven population groups (minimum –maximum across the dietary surveys in **mg P/kg bw per day**)

	Infants below 16 weeks	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario							
• Mean	87	25–113	45–113	39–82	16–40	12–27	12–24
• 95th percentile	113	53–196	73–145	61–148	29–84	22–58	21–48
Refined estimated exposure assessment scenario							
Brand-loyal scenario							
• Mean	53	12.0–35.0	10.1–27.2	5.9–25.6	2.4–16.6	4.4–10.6	4.7–9.9
• 95th percentile	69	27.4–65.7	20.6–53.6	11.4–55.9	5.1–37.0	9.1–25.2	9.4–20.2
Non-brand-loyal scenario							
• Mean	48	10.2–15.8	5.5–11.1	3.7–9.9	1.4–6.8	1.8–3.7	1.7–3.2
• 95th percentile	62	21.5–38.9	12.6–21.2	7.3–26.5	3.0–17.1	3.6–8.2	3.1–7.1

bw: body weight.

In the *regulatory maximum level exposure assessment scenario*, the mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives ranged from 198 mg P/person per day in infants (> 12 weeks) to 1,945 mg P/person per day in adolescents. The high (95th percentile) exposure ranged from 419 mg/person per day in infants (> 12 weeks) to 3,638 mg/person per day in adults.

In the *brand-loyal refined estimated exposure scenario*, the mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives ranged from 96 mg P/person per day in infants (> 12 weeks) to 747 mg P/person per day for the elderly, and the high exposure (95th percentile) from 203 mg P/person per day in toddlers to 1,600 mg P/person per day for adolescents, adults and the elderly. In the *non-brand-loyal scenario*, mean exposure ranged from 69 mg P/person per day in children to 298 mg P/person per day in adolescents, and the high exposure from 135 mg P/person per day in children to 749 mg P/person per day in adolescents.

Exposure estimated for infants below 16 weeks of age was between 349 mg P/person per day at the mean and 454 mg P/person per day at the high level (95th percentile) when using the MPLs (*regulatory maximum level exposure assessment scenario*). In the *refined estimated exposure scenario*, the mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives was estimated at 213 mg P/person per day at the mean and 278 mg P/person per day at the high level for the brand-loyal scenario while for the non-brand-loyal scenario, the estimates were 192 mg P/person per day at the mean and 250 mg P/person per day at the high level.

In the *refined estimated exposure scenario taking into account the foods for special medical purposes (FSMP)* for infants and toddlers, mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives ranged for infants between 111 and 209 mg P/person per day and between 66 and 157 mg P/person per day for toddlers. The 95th percentile of exposure to phosphates (E 338–341, E 343, E 450–452) ranged for infants between 199 and 463 mg/person per day and for toddlers between 201 and 217 mg/person per day. Results of infants and toddlers exposure expressed per kg bw are presented in the table below (Table 6).

Table 6: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives for FSMP consumers only, in infants and toddlers (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Infants (< 16 weeks)	Infants (12 weeks–11 months)	Toddlers (12–35 months)
• Mean	87	13–29	4–14
• 95th percentile	113	26–76	17–20

bw: body weight.

For the *food supplements consumers only*, mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives ranged from 275 mg P/person per day for children to 1,541 mg P/person per day for the elderly. The 95th percentile of exposure to phosphates (E 338–341, E 343, E 450–452) ranged from 753 mg P/person per day for adolescents to 7,292 mg P/person per day for adults. The Panel noted the high levels for food supplements compared to therapeutic use (see Section 3.8.1). According to data providers, in a number of cases, the phosphates are added principally as nutrient substance and not as additives. However, in other cases, the addition of phosphates (e.g. higher reported use levels) is due to their technical requirements as food additives rather than an intended use as nutrient sources. The Panel noted the high intakes resulting from such levels and the potential risk for people who might consume food supplements regularly.

Results of children, adolescents, adults and the elderly exposure expressed per kg bw are presented in the table below (Table 7).

Table 7: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives for food supplements consumers only, in children, adolescents, adults and the elderly (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
• Mean	15–89	8–23	6–22	10–24
• 95th percentile	38–112	21–26	20–99	24–83

bw: body weight.

Main food categories contributing to exposure to phosphates (E 338–341, E 343, E 450–452)

The main food categories contributing to the total exposure to phosphates (E 338–341, E 343, E 450–452) as food additives presented below are extracted from the results expressed in mg P_2O_5/kg bw per day (Appendix L).

Main food categories contributing to exposure to phosphates (E 338–341, E 343, E 450–452) using the regulatory maximum level exposure assessment scenario

In the *regulatory maximum level exposure assessment scenario*, the main contributing food categories to the total mean exposure estimates for infants were infant formulae and processed cereal-based foods and baby foods. For toddlers, fine bakery wares are the main contributing food category, while for children, fine bakery wares and Unflavoured pasteurised and sterilised (including UHT) milk are the main contributing food categories. For all other populations, the main contributing food categories are bread and rolls and fine bakery wares.

Main food categories contributing to exposure to phosphates (E 338–341, E 343, E 450–452) using the refined exposure assessment scenario

In the *brand-loyal refined estimated exposure scenario*, the main contributing food categories to the total mean exposure estimates for infants were infant formulae and processed cereal-based foods and baby foods. For the other populations – toddlers, children, adolescents, adults, the elderly – the main contributing food categories are bread and rolls and fine bakery wares. Meat products are the third contributing food categories for adults and the elderly.

In the *non-brand-loyal refined estimated exposure scenario*, the main contributing food categories to the total mean exposure estimates for infants were infant formulae and processed cereal-based foods and baby foods. As for the *brand-loyal scenario*, for the other populations – toddlers, children, adolescents, adults, the elderly – the main contributing food categories are bread and rolls and fine bakery wares. Added to these, processed cheese is also an important food contributing category for toddlers; and for children, adults and the elderly, meat products and sugars and syrups (as defined by Directive 2001/111/EC) are also important food contributing categories.

Dietary exposure to phosphates (E 338–341, E 343, E 450–452) considering the proposed extension of use

Tables 8a,b summarises the estimated exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in six population groups (Table 4) taken into account the proposed extension of use on the FC 05.2 'Other confectionary including breath refreshing microsweets' according to the different exposure scenarios. Results are presented in mg phosphorus (P)/person and per day and mg P/kg bw per day. Results in mg P_2O_5/person and per day and mg P_2O_5/kg bw per day are available in the appendixes to the opinion (Appendix M.1). Detailed results per population group and survey are also presented in Appendix M.2.

Table 8a: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in the regulatory maximum level exposure assessment scenario and in the refined exposure assessment scenarios, in six population groups (minimum–maximum across the dietary surveys in **mg P/person per day**) considering the proposed extension of use

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario considering the extension of use in FC 05.2 only						
• Mean	198–998	446–1,555	725–1,751	857–1,945	850–1,867	890–1,848
• 95th percentile	419–1,714	754–2,052	1,070–2,959	1,461–3,462	1,530–3,638	1,510–3,551
Refined estimated exposure assessment scenario considering extension of use in FC 05.2						
Brand-loyal scenario						
• Mean	96–309	101–372	108–620	130–733	319–722	337–747
• 95th percentile	222–570	203–745	215–1,291	287–1,603	658–1,600	683–1,559
Non-brand-loyal scenario						
• Mean	81–141	78–152	69–237	74–298	126–278	121–241
• 95th percentile	191–253	153–266	135–613	155–749	253–636	212–480

Table 8b: Summary of dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives in the regulatory maximum level exposure assessment scenario and in the refined exposure assessment scenarios, in six population groups (minimum–maximum across the dietary surveys in **mg P/kg bw per day**) considering the proposed extension of use

	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario considering the extension of use in FC 05.2 only						
• Mean	25–113	45–113	39–82	16–40	12–27	12–24
• 95th percentile	53–196	73–145	61–148	29–84	22–58	21–48
Refined estimated exposure assessment scenario considering extension of use in FC 05.2						
Brand-loyal scenario						
• Mean	12.0–35.0	10.1–27.2	5.9–25.6	2.4–16.6	4.4–10.6	4.7–9.9
• 95th percentile	27.4–65.7	20.6–53.6	11.4–55.9	5.1–37.0	9.1–25.2	9.4–20.2
Non-brand-loyal scenario						
• Mean	10.2–15.8	5.5–11.1	3.7–9.9	1.4–6.8	1.8–3.7	1.7–3.2
• 95th percentile	21.5–38.9	12.6–21.2	7.3–26.5	3.0–17.1	3.6–8.2	3.1–7.1

bw: body weight.

While for the current authorisation, confectionery with added sugar were included, the proposed extension of use was considered by including the FC 05.2 confectionery without added sugar. The latter

category represents a small consumption level. Added to the low use level for the food category 05.2 of confectionary and the high number of authorised uses taken into account in the assessment, it should explain the fact that no difference is noticed in the exposure estimates with the proposed extension of use.

Uncertainty analysis

Uncertainties in the exposure assessment of phosphates (E 338–341, E 343, E 450–452) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2007), the following sources of uncertainties have been considered and summarised in Table 9.

Table 9: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[(a)]
Consumption data: different methodologies/representativeness/underreporting/misreporting / no portion size standard	+/–
Methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/–
Uncertainty in possible national differences in use levels of authorised uses	+/–
Reported use levels:	
– reported use levels converted in P_2O_5 based on anhydrous form in food categories 15.1 and 17, for which the form was not specified	+
– use levels considered applicable to all foods within the entire food category, whereas on average 9.6% of the foods, belonging to food categories with foods labelled with additive, was labelled with the additive	+
The 57 authorised uses which were taken into account in the refined exposure assessment scenarios out of all authorised uses (N = 108), corresponded to 30% to 93% of the amount (g of foods by body weight) of food consumption documented in the EFSA Consumption Database	–
Foods selected for the exposure assessment: exclusion of authorised uses due to missing FoodEx linkage (n = 15/total number of authorised uses)	–
Foods selected for the exposure assessment: inclusion of authorised uses without considering the restriction/exception (n = 7/total number of authorised uses)	+
Foods included in the exposure assessment: no data for certain authorised uses which were therefore not considered in the refined exposure estimates (n = 11/total number of authorised uses)	–
Foods which may contain the food additive according to Annex III to Regulation (EC) No 1333/2008 not taken into account	–
Regulatory maximum level exposure assessment scenario:	
– exposure calculations based on the MPL according to Annex II to Regulation (EC) No 1333/2008	+
Refined exposure assessment scenarios:	
– exposure calculations based on the maximum (in the brand-loyal scenario only) or mean levels (reported use from industries, in both brand-loyal and non-brand loyal scenario)	+/–

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Phosphates (E 338–341, E 343, E 450–452) are authorised for 108 uses. The Panel calculated that out of the foods authorised to contain phosphates (E 338–341, E 343, E 450–452) according to Annex II to Regulation (EC) No 1333/2008, 30% (for children) to 93% (for infants) of the amount of food consumed (by weight) per population group was reported to potentially contain phosphates (E 338–341, E 343, E 450–452) as a food additive.

Data were received on most of the food categories in which the food additives are authorised to be added (no data for unprocessed fish, molluscs and crustaceans, alcoholic beverages, breakfast cereals, butter, salts).

The Panel noted that information from the Mintel GNPD (Appendix H) indicated that phosphates (E 338–341, E 343, E 450–452) were labelled on 134 food subcategories, categorised according to the

Mintel GNPD nomenclature. Most of these food subcategories were included in the current exposure assessment, as only approximately 1.5% of the foods (from 10 different food subcategories) labelled with phosphates from Mintel were not taken into account in the assessment.

The percentage of foods per Mintel subcategory labelled to contain phosphates (E 338–341, E 343, E 450–452) was on average of 9.6%. For eight subcategories, the percentage of foods labelled with phosphates (E 338–341, E 343, E 450–452) was above 45%. In the assessment, it was assumed that 100% of the foods belonging to an authorised food category contained the additive. The Panel noted that the information from the Mintel GNPD indicated that phosphates (E 338–341, E 343, E 450–452) are used in a large range of foods. Therefore, an exposure assessment based on the premise that all of the foods contain phosphates would probably lead to an overestimation of the dietary exposure which represents the largest uncertainty.

The Panel noted that foods which may contain phosphates (E 338–341, E 343, E 450–452) due to carry-over (Annex III, Parts 1, 2, 3, 4, 5) were not considered in the current exposure assessment.

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to phosphates (E 338–341, E 343, E 450–452) from their use as food additives according to Annex II in European countries considered in the EFSA European database for the regulatory maximum level exposure scenario. For the refined estimated exposure scenario, uncertainties would also lead to an overestimation of exposure to phosphates (E 338–341, E 343, E 450–452).

3.4.2. Exposure to total phosphorus via the diet

Exposure to total phosphorus from the diet was estimated using analytical data. This exposure estimate is calculated using the mean/median, whichever is higher, of analytical levels for all food categories. This scenario was chosen to be representative of wider range of samples taken from the market as well as the long-term intake. This calculation covers all dietary intake of phosphorus including that emanating from other food additives containing phosphorus, as well as the use of phosphates (E 338–341, E 343, E 450–452) according to Annex III of Regulation No 1333/2008 (carry-over).

Analytical levels provided by the Member States reflect the levels of phosphorus in foods whatever the origin (from natural and other dietary sources). Therefore, the exposure estimated with analytical data should reflect more closely what is ingested through the diet including phosphorus-containing food additives added for other technological reasons. While these limited analytical data covered most of food categories from the diet, they were provided only by 10 Member States. Nonetheless the Panel assumed that these estimates were indicative of dietary exposure to phosphorus in European countries considered in the EFSA European database via the whole diet (from natural and other dietary sources).

For some food categories for which no analytical data were available, reported use levels were used in order to cover in a more exhaustive way foods in which phosphates can be present. This is the case for chewing gum (FC 05.3) and sugars and syrups as defined by Directive 2001/11/EC (FC 11.1).

Tables 10a,b summarise the estimated exposure to phosphates from the diet in seven population groups (Table 4). Results are presented in mg phosphorus (P)/person and per day and in mg P/kg bw per day. Detailed results per population group and survey (in mg P/kg bw per day and mg P/person per day) are also presented in Appendixes N.1 and N.2.

Table 10a: Summary of dietary exposure to phosphorus from the diet,* in seven population groups (minimum–maximum across the dietary surveys in mg P/person per day)

	Infants (< 16 weeks)	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
• Mean	254	251–577	693–1,032	798–1,363	986–1,573	1,204–1,625	1,185–1,561
• 95th percentile	331	451–964	1,069–1,388	1,169–2,008	1,505–2,427	1,829–2,728	1,743–2,619

*: Using analytical data except for chewing-gum (FC 05.3) and sugars and syrups (FC 11.1).

Table 10b: Summary of dietary exposure to phosphorus from the diet,* in seven population groups (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Infants (< 16 weeks)	Infants (12 weeks–11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
• Mean	64	32–85	55–74	33–62	18–33	16–22	16–20
• 95th percentile	83	56–106	85–123	55–92	31–56	25–36	24–35

bw: body weight.
*: Using analytical data except for chewing-gum (FC 05.3) and sugars and syrups (FC 11.1).

In the *estimated exposure scenario based on analytical data*, the mean exposure to phosphates ranged from 16 mg P/kg bw per day for adults and the elderly to 85 mg P/kg bw per day for infants, and the high exposure (95th percentile) from 24 mg P/kg bw per day for the elderly to 123 mg P/kg bw per day for toddlers (Table 10b). For infants below 16 weeks of age exposure was estimated to be 64 mg P/kg bw per day at the mean and 83 mg P/kg bw per day at the high level (95th percentile).

Main food categories contributing to exposure to phosphates using analytical data

In this scenario, the main contributing food categories to the total mean exposure estimates for infants were unflavoured pasteurised and sterilised (including UHT) milk, infant and follow-on formulae. For the other populations – toddlers, children, adolescents, adults, the elderly – the main contributing food categories are unflavoured pasteurised and sterilised (including UHT) milk, bread and rolls and meat products (Appendix O).

Specific scenarios

The specific scenarios on food supplements and FSMP were also performed. As no analytical data for food supplements and foods for special medical purposes for infants and toddlers (FCs 13.1.5.1 and 13.1.5.2) were available, maximum levels for these food categories were taken from the reported use levels from industry for estimating exposure of FSMP consumers only and food supplements consumers only.

Table 11: Summary of dietary exposure to phosphorus for FSMP consumers only from the diet,* in infants and toddlers (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Infants (< 16 weeks)	Infants (12 weeks–11 months)	Toddlers (12–35 months)
• Mean	154	35–75	55–78
• 95th percentile	200	65–133	81–112

bw: body weight.
*: Phosphorus is also present in other sources (e.g. milk).

For the FSMP food categories (i.e. FCs 13.1.5.1 and 13.1.5.2), reported use levels were submitted by industry when phosphates are added as food additives but also as nutrients. For the FSMP scenario performed with the reported use levels only (Section 3.4.1), only the levels provided for the need of phosphates as food additives were used. In the current FSMP scenario, also the use levels reported for the addition of phosphates as nutrients were considered.

Estimates for the infants and toddlers consumers only of foods for special medical purposes ranged at the mean from 35 mg P/kg bw per day for infants (12 weeks–11 months) to 154 mg P/kg bw per day for infants below 16 weeks (Table 11). At the high level, exposure ranged from 65 mg P/kg bw per day for toddlers to 200 mg P/kg bw per day for the infants below 16 weeks. As mentioned above, this scenario is related to the infants and toddlers consumers only of FSMP, eating foods at mean concentration of phosphorus except for the FCs 13.1.5.1 and 13.1.5.2 for which the maximum reported use levels were used instead.

Table 12: Summary of dietary exposure to phosphorus for food supplements consumers only from the diet, in children, adolescents, adults and the elderly (minimum–maximum across the dietary surveys in mg P/kg bw per day)

	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
• Mean	53–138	31–48	25–40	25–42
• 95th percentile	84–153	58–62	44–121	41–97

bw: body weight.

This scenario focused on the specific population of food supplement consumers only. Estimates ranged from 1,280 mg P/person per day for children to 2,839 mg P/person per day for elderly, at the mean; and from 1,958 mg P/person per day for the children to 8,923 mg P/person per day for adults, at the high level. The mean concentration of phosphorus from the diet was considered background. Dietary exposure is estimated from food supplements intake, assuming all food supplements contain phosphates, at the maximum reported use level combined with the background. Uncertainty linked to the lack of knowledge on the form of calcium phosphates as mentioned in the food supplements' consumers only scenario (page 35) also apply to the above estimates. For these reasons, this scenario reflects a conservative exposure estimate to phosphorus.

Uncertainty analysis for the general analytical data

Exposure intakes of phosphorus through the whole diet are subject to the same uncertainties concerning the food consumption data than the exposure estimates of phosphates (E 338–341, E 343, E 450–452) as food additives (as mentioned in Table 9). Uncertainties to which types of food the analytical levels refer to is another uncertainty which applies to intakes of phosphorus through the whole diet. Apart for the methodology used to estimate high percentiles (95th) long-term (chronic) exposure based on data from food consumption surveys covering only a few days which should result in an overestimation of the exposure intakes, the other uncertainties linked to consumption data could results in both under or overestimation of the true exposure to phosphates though the whole diet.

Finally, some food categories were not taken into account as no data were available (processed eggs, salts and some alcoholic beverages). This would lead to an underestimate of the total intake; however, considering the food categories missing, the underestimation in that case of the general population should be low.

3.4.3. Exposure via other sources

Phosphates are also used in cosmetic products and in medications as an active pharmaceutical ingredient, or as a counter-ion for drugs or mostly as an excipient. Quantification of exposure via all these sources is not precisely known and could therefore not be taken into account in this opinion.

3.5. Biological and toxicological data

Phosphorus only occurs in the body as its pentavalent form bound to oxygen as phosphate. As such it occurs in organic and inorganic forms. Phosphate is essential for all living organisms. The intracellular activity of phosphate ions participates in acid base balance. Phosphate is intrinsically involved with regulation of metabolic processes via phosphorylation of proteins and supplying energy by means of nucleotides triphosphates (e.g. ATP, GTP, CTP and UTP) which serve as energy depots supporting protein and polysaccharide synthesis, ion pumps, cell signalling, muscle contractility. Phosphate is also component of second messengers such as cyclic adenosine monophosphate (cAMP), inositol polyphosphates (IP3) and cyclic guanine monophosphate (cGMP). Phosphate is fundamental for the structure and function of DNA and ribonucleic acid (RNA). Phospholipids are part of cell membrane structure where they affect the membrane fluidity and function. In erythrocytes, 2–3 diphosphoglycerate modulates the release of oxygen from haemoglobin in tissues (Frausto da Silva and Williams, 2001).

The whole human body P content is 500–700 g; it varies with skeletal mass which is higher in men. Fifteen percent of the phosphate in the body is involved in the above-mentioned metabolic function and control, whereas the largest pool of phosphates (approximately 85%) is found together with calcium in the skeleton.

Free phosphate is found in both intracellular and extracellular fluid (ECF). Approximately 85% of P in the ECF is present as HPO_4^{2-} and $H_2PO_4^-$ (4:1 ratio). These anions are important for acid-base

regulation and their relative amounts and association with cations are pH dependent. The ratio between the two ionised phosphate forms is integral to the control of P and of Ca absorption, distribution, excretion and bone deposition. In some instances, inappropriate mineralisation can occur in soft tissues such as the kidneys and cardiovascular structures. This pathological process is called biomineralisation.

Biomineralisation is sensitive to the saturation of ECF (plasma and interstitial fluid) with hydroxyapatite ($Ca_5(PO_4)_3OH$) and its precipitation at foci for crystallisation, however the process and its regulation are not fully understood (Tavafoghi and Cerruti, 2016). Hydroxyapatite is the predominant salt in the ECF at physiological pH and pCO_2 and the activity product (Ca X P) of ionised calcium (1.1–1.3 mmol/L) and P (0.9–1.4 mmol/L) approximates to 1.3 $mmol^2/L^2$. It has been suggested that when this value exceeds by approximately twofold the solubility constant of hydroxyapatite, the salt precipitates at crystallisation foci. This may occur when serum phosphate exceeds 2.4–2.5 mmol/L. The higher serum levels of P and Ca in early life compared with those of adulthood are seen to be consistent with the concept that they support physiological skeletal mineralisation (Heaney, 2012). It has been proposed that carbonated hydroxyapatite is the form involved in mineralisation and that charged amino acids in non-collagen proteins, via binding of Ca^{2-} and PO_4^{3-}, and possibly localised supersaturation of hydroxyapatite, induce nucleation and crystal precipitation, leading to tissue mineralisation (Tavafoghi and Cerruti, 2016). High phosphorus intake (3,000 mg phosphorus per person per day on top of the diet) may disrupt the hormonal regulation of phosphorus, calcium and vitamin D (Calvo and Uribarri, 2013). This imbalance may contribute to bone loss and consequently the increased risk of osteoporosis and bone fractures (Calvo and Lamberg-Allardt, 2017). Further discussion on interaction between phosphorus and other minerals can be found in EFSA 2013.

Phosphates which occur naturally in food are absorbed throughout the duodenum and jejunum, but principally in the duodenum and jejunum with an efficiency of between 55 and 90% of the amount and source of dietary phosphate and vitamin D status (Sabbagh et al., 2011). In the intestinal lumen, inorganic phosphate is released from the food by phosphatases at a rate that depends on the chemical complexity of the organic phosphates. Phosphate from phytates (myoinositol esaphosphate) is poorly released. The formation of complexes between dietary phytates, calcium, magnesium and some amino acids mutually reduce their availability for intestinal uptake (Cheryan, 1980). The bioavailability of phosphate from phytates is poor (20–30%) due to the lack of the enzyme phytase in humans. Generally, the availability for net phosphate absorption might be limited by the calcium content of the diet (Heaney and Nordin, 2002; Sabbagh et al., 2011; Heaney, 2012; O'Brien et al., 2014; Scanni et al., 2014). Other factors including epidermal growth factor, glucocorticoids, oestrogens, acid base balance and phosphatonins potentially influence the absorption of phosphates either directly or indirectly (Penido and Alon, 2012).

It has been proposed that since dietary phosphates arising from food additives are in an inorganic forms they do not require release by luminal phosphatases and could be taken up and absorbed more efficiently than organic phosphate from animal or plant foods (Kalantar-Zadeh et al., 2010). The major determinant of systemic phosphate homeostasis is renal handling of phosphate, namely the amount of phosphate ultrafiltered by the glomerulus and the amount that is reabsorbed at tubular level. Urinary loss of phosphate is the major route of phosphate excretion and under normal physiologic conditions the renal phosphate transporter threshold is the main determinant of phosphate plasma levels.

Factors influencing renal loss of phosphate are parathyroid hormone (PTH), Klotho and fibroblast growth factor-23 (FGF-23) while calcitriol is the major factor regulating intestinal phosphate absorption.

Under normal conditions, serum phosphate levels show the highest values in the first months of age (2.38 $\pm$ 0.54 mmol/L corresponding to 7.4 $\pm$ 1.7 mg/dL at 1 month, 2.21 $\pm$ 0.43 mmol/L corresponding to 6.9 $\pm$ 1.3 mg/dL at 3 month of age) while it significantly decreased at 6 month (1.80 $\pm$ 0.41 mmol/L corresponding to 5.6 $\pm$ 1.3 mg/dL) (Bistarakis, 1986). Subsequently, serum levels progressively decrease during childhood to achieve the average adult reference values of approximately 1.0 mmol/L (corresponding to 3.2 mg/dL) by the age of 16 years (Alon, 1994). This pattern has been attributed to higher renal tubular phosphate reabsorption in infants and children occurring to maintain the rapid body growth and calcification of the skeleton.

3.5.1. Absorption, distribution, metabolism and excretion

Human studies

Absorption

Inorganic phosphate used as food additives assessed in this opinion is assumed to dissociate in the gastrointestinal lumen. The released phosphate is well absorbed mainly as free orthophosphate in the

small intestine with amounts ranging between 55 and 90% of the dose (Sabbagh et al., 2011; Heaney, 2012; O'Brien et al., 2014; Scanni et al., 2014). Several factors regulate the phosphate absorption among them calcitriol, PTH epidermal growth factor, glucocorticoids, oestrogens, metabolic acidosis, phosphatonins and secreted frizzled-related protein 4 (sFRP-4) (Penido and Alon, 2012). Intestinal phosphate absorption occurs by passive diffusion (McHardy and Parsons, 1956) and sodium-dependent active transport (Walton and Gray, 1979; Eto et al., 2006). There are different sodium transporters in the body [NaPi-IIa (SLC34A1), NaPi-IIb (SLC34A2 or NPT2b) and NaPi-IIc (SLC34A3)]. NaPi-IIb is predominant in the intestine (Penido and Alon, 2012; Biber et al., 2013) and its activity is modulated by active vitamin D and by a low phosphorus diet (Segawa et al., 2005; Forster et al., 2011; Sabbagh et al., 2011).

Phosphorus availability for intestinal absorption may be limited by the calcium content of the diet (Sabbagh et al., 2011; Heaney, 2012; O'Brien et al., 2014; Scanni et al., 2014).

Atkinson et al. (1995) reviewed data on the P content of human breast milk and reported this to be between 160 mg/L at 14 days, 140 mg/L at 30 and 90 days and 120 mg/L at 180 days post-partum. Neonatal absorption of phosphorus is between 86% and 97% irrespective of calcium or phosphorus intakes (Loughead and Tsang, 1998; Kovacs, 2015).

Distribution

Phosphorus is distributed throughout the body with the largest pool (approximately 85% of body content) together with calcium in the skeleton as hydroxyapatite.

Excretion

About 200 mmol of P is filtered daily by the glomerulus of which 80% or more is reabsorbed in proximal tubules. The tubular uptake of P is mediated via sodium phosphate co-transporters, in particular NaPi-IIa, characterised by a threshold known as the tubular maximum for P (TmP) (Tenenhouse, 2005). PTH and FGF-23 with Klotho influence the re-absorption rate of the ultrafiltrated P. In steady-state conditions, the amount of phosphorus excreted in the urine equals or is close to the amount of dietary phosphorus absorbed by gut (Berndt and Kumar, 2009; Scanni et al., 2014). However, in the real practice, a single urinary P measurement is not believed as a validated marker of dietary exposures in free living populations (Cupisti and Gallieni, 2018; Stremke et al., 2018). Osgood and Ivey reported that the concentration of P^{32} in plasma after intravenous injection had a mean half-life of 8.5 days in patients with leukaemia (Osgood et al., 1950). Faecal losses of P result from non-absorbed dietary phosphorus, mostly represented by phytate (Greger et al., 1978; Anderson, 2005; Delgado-Andrade et al., 2011), and from digestive secretions (0.9–4 mg/kg bw per day) (O'Brien et al., 2014).

In summary, the inorganic phosphorus deriving from food additives is mainly absorbed as free orthophosphate. The amount of orthophosphate absorbed is about 80–90%. Excretion is via the kidney through glomerular filtration and tubular handling. Data are available on the kinetics of disodium diphosphate, trisodium diphosphate, tetrasodium diphosphate and tetrapotassium diphosphate but not on dicalcium diphosphate and calcium dihydrogen diphosphate.

Animal studies

The absorption of P^{32}-radiolabelled tetrasodium diphosphate, sodium tripolyphosphate, sodium polyphosphate and sodium hexametaphosphate was investigated in rats by measuring the blood, liver, stomach, brain, intestine and bones concentration of P^{32} by radiochromatography (Schreier and Noller, 1955). The lower molar mass compounds were absorbed more rapidly than those with a higher molar mass. At 18 h, more than 60% of the sodium hexametaphosphate was still found in the intestinal tract. Radioactive orthophosphate and a small amount of diphosphate were present in the blood. The authors stated that high polymeric phosphates do not penetrate the intestinal wall readily; however, the diphosphate is hydrolysed into orthophosphate at neutral pH.

Tetrasodium diphosphate absorption was measured in the rats after 3 weeks continuous treatment via diet. Food consumption was determined and the faeces and urine collected in the 5% tetrasodium diphosphate group over a 6-day period from five male animals (Datta et al., 1962). In another study part, faeces and urine were collected over a 3-day period from five male animals having treated for 8 weeks with 5% tetrasodium diphosphate and from five male animals having treated for 8 weeks with 5% sodium orthophosphate in the diet. Food, urine and faeces were analysed for calcium and diphosphate. Diphosphate was not detected in rat faeces or urine; however, orthophosphate was found in the urine so that it can be concluded that diphosphate was almost completely hydrolysed to orthophosphate in the rat gut and the resulting orthophosphate was well absorbed (approximately 85%) from the gastrointestinal tract.

There are no data on the toxicokinetics (TK) of dicalcium diphosphate and calcium dihydrogen diphosphate.

3.5.2. Measurements of intake and exposure in humans

Markers of exposure in humans need to be evaluated in the context of the risk assessment of phosphates. There are several indicators used to characterise the exposure in epidemiological studies all of which have considerable limitations.

Dietary intake

Different dietary assessment methods have been used in the epidemiological studies to measure phosphorus intake from diet. Three studies (Alonso et al., 2010; Yamamoto et al., 2013; Kwak et al., 2014) have used food frequency questionnaires (FFQ) to measure the phosphorous intake while one study also used 3 days food record (Itkonen et al., 2013).

All the dietary assessment methods rely on food composition tables to give the amount of phosphorus in each food item. The food composition tables give most often one value for each food item, and thereby do not distinguish between naturally occurring phosphorus and that from food additives. There can be large variation in the phosphorus level in the same type of food (Benini et al., 2011; Trautvetter et al., 2018). Total phosphorus concentrations have been shown to be up to twofold higher in food items with phosphorus additives, compared with additive free products (Karalis and Murphy-Gutekunst, 2006; Benini et al., 2011).

Dietary records and 24-h dietary recalls are open-ended dietary assessment methods and single 24-h dietary recalls are not sufficient to estimate chronic phosphate intake reliably (Cupisti and Gallieni, 2018; Stremke et al., 2018). More than one 24-h dietary recall is needed to assess exposure (EFSA, 2014).

FFQ are closed methods. To be able to capture phosphorus rich foods, the questionnaires have to be design considering this specific goal. Only one of the studies using FFQ gives an energy-adjusted correlation coefficient of 0.51 for phosphorus compared with several 24-h recalls (Kwak et al., 2014). Both methods used the same food composition table.

Serum/plasma phosphorus concentration

The reference range for serum phosphorus is 0.8–1.5 mmol/L (2.7–4.5 mg/dL) in adults and 1.3–2.3 mmol/L (4.0–7.0 mg/dL) in children (more details in introduction to Section 3.5).

In the NHANES III study (1988–1994) dietary intake of phosphorus, encompassing 15,513 participants, was assessed by 24-h dietary recall and in addition a questionnaire for 1-month food frequency was used (NHANES III, 1988–1994). The data were used by de Boer et al. (2009) to investigate the relationship between dietary phosphorus intake and single measurement of serum phosphorus concentration. A statistically significant relationship was found between the two parameters, with each 500-mg/day increment in phosphorus intake being associated with an increase of 0.03 mg/dL in serum phosphorus ($p < 0.001$), after adjustment for age, sex, race, time of measurement and fasting status. A further study with fewer participants (N = 3,421) did not find any relationship between phosphorus intake and serum phosphorus concentration (Mataix et al., 2006). Serial measurements throughout the day and subsequent averaging the values would result in a better estimate of phosphorus exposure (Portale et al., 1987; Calvo and Heat, 1988; Kemi et al., 2006).

Moore et al. (2015) conducted a cross-sectional study using data from the NHANES to investigate the association between food sources rich in organic phosphorus and foods rich in inorganic phosphate from additives and serum phosphorus levels. A total of 7,895 subjects, aged 20–85 years (mean 46.7, SD = 0.5 years), not pregnant and with no missing data on laboratory values for serum phosphorus, urine creatinine and albuminuria as well as dietary data were included in the study. Demographic, clinical and dietary data (24-h food recall) was obtained for all participants. Population mean age and the mean serum phosphorus was 46.7 years (SD = 0.5) and 3.81 mg /dL (SD = 0.01), respectively. Phosphorus content of foods was categorised as organic and inorganic. High serum phosphorus was associated with high consumption of dairy foods categorised as containing inorganic phosphates ($p = 0.0097$) after controlling for estimated glomerular filtration rate (eGFR), body mass index (BMI; in kg/m^2) and albumin-to-creatinine ratio. High serum phosphate was also observed in high consumers of dairy food categorised as not containing inorganic phosphate.

Trautvetter et al. (2016) investigated the association between serum phosphate and dietary phosphorous and calcium in a double-blind, placebo-controlled study of 32 women and 30 men. Participants received dietary phosphorous (1,000 mg/day) with different amounts calcium (0, 500,

1,000 mg/day) for 8 weeks. The study did not show any association between dietary phosphate intake and fasting serum phosphorous. A high intake of phosphorous without adequate calcium did affect plasma FGF-23, although with a large interindividual variability which makes it unsuitable as a surrogate marker of intake.

Karp et al. (2013) investigated the effect of dietary phosphorous on calcium phosphorous metabolism in an acute (24-h), placebo-controlled cross-over study on 14 women (mean age 23 years). Participants received 1,500 mg/day phosphorous as monophosphate or polyphosphate. The results showed an acute increase in serum and urinary phosphorous following the ingestion of the phosphorous supplement, although serum phosphorous concentration returned to baseline concentrations after 24 h.

Kemi et al. (2006) investigated the acute effect of high dietary phosphorous and bone metabolism in 14 women (mean age 24 years). In a randomised, placebo-controlled cross-over study, participants received either 0, 250, 750 or 1,500 mg phosphorous, and concentrations of serum phosphate, ionised calcium and PTH were measured for 24 h. The results suggest a dose–response relationship between phosphorous intake and serum phosphorous concentration and PTH, and an inverse relationship with ionised calcium concentration. These results confirm findings from other studies that serum phosphorous concentration can be affected in the short-term by dietary intake, but do not provide information on the association with chronic or habitual intake.

At dietary phosphate intake below 20 mmol/day (619 mg/day), there is a correlation between dietary intakes and serum or plasma phosphate concentrations. However, at intakes above this, corresponding to customary intakes, the relationship is much weaker and is not indicative of intakes (Heaney, 1997).

All the studies on the association between measurements of phosphate intake by dietary assessment and serum P showed only a weak correlation in subjects with normal renal functions.

The poor relationship between phosphate intake and serum/plasma level might be partially explained by the different bioavailability of phosphate from different sources. For example, the poor release of phosphate from phytates, as well as the interaction between phytates and inorganic phosphorous (see Section 3.5.1), reduce the bioavailability of dietary phosphorous from plant foods (Schlemmer et al., 2009). Vegetarian diets with the same phosphorous content as animal-based diets therefore appear to result in a lower absorption of phosphorous and subsequently a lower serum P and urinary excretion (Moe et al., 2011). The relationship between dietary and serum phosphorous is therefore confounded not only by homoeostatic regulation of serum phosphorous, but also the dietary source and form of phosphorous.

Another factor could be underestimation of phosphate content in food due to insufficient information in food composition tables and limitations of the methods of some dietary intake measurements (EFSA, 2014).

The EFSA NDA Panel considered that single serum phosphorus concentration measurements cannot serve as surrogate for phosphorus intake (EFSA NDA Panel, 2015). The FAF Panel agreed with this position.

Urinary phosphorus excretion

The main route of phosphorus elimination is excretion in the urine the mechanisms being glomerular filtration and tubular reabsorption in the kidney. Hence, urinary phosphorus excretion is a surrogate for phosphorus intake. A 24-h collection of the urine will give a more precise estimate than measuring the concentration in a spot urine even if normalised by urine creatinine.

Urinary excretion of phosphorous has been considered to be a surrogate marker of phosphorous intake (Morimoto et al., 2014), although this is based on the assumption of a uniform and constant absorption of dietary phosphorous and its complete renal excretion (Hruska et al., 2008). However, Brixen et al. (1992) has shown that urinary phosphorous is affected by short-term changes in dietary phosphorous intake, and both Morimoto et al. (2014) and Trautvetter et al. (2018) show only weak associations between dietary phosphorous and urinary phosphorous. The study reviewed here did not show an association between urinary phosphorous excretion and increased risk of cardiovascular diseases (CVDs), but this might only reflect short-term phosphorous intake and is therefore not suitable to assess the risks associated with habitual phosphorous intake.

According to Sun et al. (2017) who evaluated the variability of a variety of urinary makers in three major surveys, it is necessary to have three times within 1 year 24-h collection of urine to provide a reasonably strong correlation with the true long-term average urinary excretion of phosphate.

The Panel considered that single spot urinary phosphorus excretion, and single 24-h urinary excretion are not valid markers for long-term dietary exposure which is in agreement with the conclusion from the NDA Panel in 2015.

FGF-23 – Marker of exposure and effect

FGF-23 is a hormone produced by osteocytes which regulates phosphate excretion by influencing the phosphate reabsorption in the kidney mediated via alpha-Klotho as a cofactor.

Some publications showed that dietary intake of phosphorus was related to the FGF-23 plasma concentration (Antoniucci et al., 2006). However, others did not find this association (Larsson et al., 2003).

FGF-23 is elevated in relation to the decline of kidney function in patients with chronic kidney disease (CKD; Larsson et al., 2003; Faul et al., 2011). Elevated FGF-23 was linked predominantly to left ventricular dysfunction and consequently to related morbidity and mortality; it likely occurs nearly exclusively in subjects with CKD in whom the FGF-23 system is strongly stimulated (reviewed in Stöhr et al., 2018). Only few studies investigated the association in subjects without renal disease and mostly in elderly patient which raises the question of the generalisability of the findings (Arnlöv et al., 2013; Brandenburg et al., 2014).

Whereas the group of Faul et al. (2011) interpreted their results obtained in patients with CKD as demonstrating that elevated FGF-23 activity/levels caused left ventricular hypertrophy (Grabner et al., 2015; Leifheit-Nestler et al., 2016) novel findings challenges this interpretation. Recent data allow the interpretation that FGF-23 is locally produced and released by myocytes in the event of (acute) myocardial damage.

When considering whether FGF-23 could be used as a marker to determine the safe level of phosphate intake it has to be considered that the role of FGF-23 for negative influences on cardiac function is not yet established as in a recent review (Stöhr et al., 2018) the authors concluded: 'Prior to any therapeutic intervention with the aim to minimize potentially negative FGF-23 effects upon cardiac structure and function, research needs to focus on and clarify relevant unsolved issues. Just to name a few, the community needs to prove how cardiac disease induces (rather than follows) FGF-23 secretion, to what degree cardiomyocytes may themselves produce FGF-23 in health and disease, whether such locally produced FGF-23 has a physiological role in (acute) myocardial damage; and whether or not (systemic) FGF-23 excess itself directly drives the development of myocardial damage'.

Furthermore, a clear dose–response relationship between phosphate intake and plasma concentration of FGF-23 has not been established. This does not allow to estimate the phosphate intake when FGF-23 levels were measured in clinical studies with cardiac endpoints.

Hence, the Panel decided that FGF-23 levels could not be used as an endpoint to assess the adverse health effects of phosphate.

3.5.3. Toxicology

There are numerous toxicology studies available with most of the phosphates used as food additives. However, the studies are generally quite old and not performed according to current guidelines. Furthermore, cations of the phosphates are constituents of human tissues that occur naturally in food stuffs, and intake of them does not cause adverse human health effects, providing that the intake isn't so high as to disturb the homeostatic mechanisms controlling the electrolyte balance of the body. Therefore, the toxicity of the cations is not discussed in this opinion.

Furthermore, in all animal studies, the phosphates were added in addition to any phosphate present in the diet. In order to calculate the doses administered over time (mg/kg bw per day) relevant conversion factors from the EFSA guidance on selected default values were used (EFSA, 2012).

The Panel recognise that where the purity details of the test material(s) used in the studies below are not stated, there will be an uncertainty associated with the true amount of phosphate used in test dosages. The exact amount of phosphate was unknown because in some toxicological studies it was not stated whether the test material used was in the anhydrous form or one of the several hydrated forms. The EU (and JECFA) additive specifications for phosphates (Appendix E) prescribe a range for the purity assay expressed as P_2O_5, which provides an indication of the purity limits. Moreover, the specifications for certain phosphates reveal several synonyms for the materials, which appear to be historically interchangeable through these and other studies. In the light of this, dosage levels have been recalculated on an anhydrous basis.

3.5.4. Acute toxicity

There are acute oral toxicity studies with all phosphates under evaluation. Available data are summarised below.

Phosphoric acid

Phosphoric acid was administered to Sprague–Dawley rats at doses between 2,510 and 6,310 mg/kg. The LD_{50} value was estimated to be more than 3,500 mg/kg (Randall and Robinson, 1990).

Magnesium phosphates

In an unpublished report from Food and Drug Research Laboratories (1973), cited in (JECFA, 1982b), a LD_{50} value of 4,600 mg/kg was reported when monocalcium phosphate was administered orally to mice and 2,170 mg/kg when administered to rats.

When tricalcium phosphate was tested for acute oral toxicity in female Wistar rats the LD_{50} value was estimated to be greater than 2,000 mg/kg bw (Harlan-Laboratories-Ltd, 2010a)

Sodium and potassium phosphates

A LD_{50} value of 3,700 mg/kg bw was reported when monosodium phosphate was administered orally to mice, and 4,100 mg/kg bw when administered orally to rats (unpublished report from Food and Drug Research Laboratories (1975), cited in (JECFA, 1982b).

A LD_{50} value for the guinea pig was reported to be 2,000 mg/kg bw when monosodium phosphate was administered orally (Eichler, 1950), cited in (JECFA, 1982b).

A LD_{50} value of 3,200 mg/kg bw was reported when monopotassium phosphate was administered orally to mice and 2,820 mg/kg bw when administered to rats (unpublished report from Food and Drug Research Laboratories (1975), cited in (JECFA, 1982b)**.**

Diphosphates

In an acute oral toxicity study where disodium diphosphate was administered to fasted adult male Swiss Webster mice and adult male Sprague–Dawley rats LD_{50} values of 2,300 mg/kg bw in mice and 1,800 mg/kg were reported (Newell et al., 1974).

In another acute oral toxicity study, Sprague–Dawley rats were administered tetrasodium diphosphate at a dose of 2,000 mg/kg bw (Seo et al., 2011). No deaths or clinical signs of toxicity were observed up to 14 days after dosing. Thus, the LD_{50} for tetrasodium diphosphate was greater than 2,000 mg/kg bw in this study.

Triphosphates

The JECFA evaluation of 1982 reports the following oral LD_{50} values for sodium triphosphate; 2,380 mg/kg bw in mouse, 1,700 mg/kg bw in rat and 2,500 mg/kg bw in rabbit, referencing Food and Drug Research Lab (1973); however, the original report which was available for review does not include the information reported by JECFA (1982b). No further detail is available for review.

Sodium triphosphate is reported to have an oral LD_{50} value of 3,210 mg/kg in mouse (Zipf, 1957). The report is a summary, with no further detail available.

Polyphosphates

The JECFA monograph (unpublished report from Food and Drug Research Laboratories 1974 cited in JECFA, 1982) reported an acute oral LD_{50} value for sodium hexametaphosphate in mice of 3,700 mg/kg bw and in rat of 2,400 mg/kg bw.

An acute oral LD_{50} of 7,250 mg/kg bw in mice has been reported for sodium hexametaphosphate (Zipf, 1957).

According to the REACH registrant, in an unpublished acute oral toxicity study, sodium metaphosphate (OECD, 2001) and sodium hexametaphosphate were administered to female Wistar rats at dose of 2,000 mg/kg bw by oral gavage. There were no deaths and no adverse findings. The LD_{50} value was concluded to be greater than 2,000 mg/kg bw.

Overall the acute oral toxicity of all evaluated phosphates is very low with LD_{50} values generally exceeding 2,000 mg/kg bw.

3.5.5. Short-term and subchronic toxicity

There are short-term and subchronic toxicology studies with most of the phosphates under evaluation. Most of the studies are quite old and of variable quality and not performed according to current guidelines.

Calcium and magnesium phosphates

A study investigated nephrocalcinosis in weanling female Wistar rats fed diets varying in concentrations of Ca and P supplied as inorganic salts (Hitchman et al., 1979). Higher phosphate and calcium percentages were obtained by adding: calcium carbonate and calcium dihydrogen phosphate or a mixture of calcium dihydrogen phosphate and monosodium phosphate to the semisynthetic diet for periods of 4–6 weeks. Treated groups were compared with control rats fed laboratory chow for the same period of time. Nephrocalcinosis was produced by semisynthetic diets with inorganic phosphate concentrations as low as 0.5% (equivalent to 600 mg/kg bw per day) on a weight basis; in contrast, rats fed regular laboratory chow showed no evidence of nephrocalcinosis. The severity of the nephrocalcinosis was proportional to dietary phosphate concentrations from 0.5 to 1.0% but other dietary constituents also altered the severity of the lesion. With a lower dietary phosphate content of 0.5%, increasing dietary Ca from 0.5 to 1.0% resulted in a decrease in the severity of the renal calcification. Decreasing protein concentrations from 25 to 15% casein increased the severity of the renal lesions ($p < 0.01$). Other dietary factors also seemed to modify the phosphate-induced nephrocalcinosis since no lesions occurred in rats on laboratory chow. The authors suggested that the availability of dietary phosphate may be a factor. The phosphate in the semisynthetic diets was totally inorganic while the natural foods of laboratory chow contain, at least in part, organic phosphate (Hitchman et al., 1979).

Sodium and potassium phosphate

Rat

Sprague–Dawley rats (weight: 60–150 g) were placed on a chow diet containing 10% disodium phosphate (equivalent to 12,000 mg/kg bw per day) for periods of 24–72 h (Craig, 1957). Some animals were killed at the end of the feeding period while other animals were placed on a control diet for 2–7 days. Animals on the experimental diet did not lose weight but developed polydipsia and high urine volume which persisted after returning to a normal diet. Kidneys were enlarged with the degree of enlargement correlated intake of food containing phosphate. Histological changes were found in the inner cortex, outer medulla and less frequently in the outer cortex of the kidneys. Histochemical changes in the form of marked deposition of minerals in the kidneys of rats kept on the diet containing an excess of inorganic phosphate were observed.

In a study by Dymsza et al. (1959), three groups with 12 male Wistar rats in each group were fed diets containing added dipotassium phosphate so that the calcium and phosphorus concentrations in the experimental diets were as detailed below.

Diet	Calcium % (mg/kg bw per day)	Phosphorus % (mg/kg bw per day)
Control	0.56 (504)	0.42 (378)
'Normal orthophosphate'	0.47 (423)	0.43 (387)
'High orthophosphate'	0.50 (450)	1.30 (1170)

bw: body weight.

The study was conducted in three stages, with experimental observations after animals had consumed the test diets for 50, 60 or 150 days. No adverse physiological effects were observed clinically at autopsy or on histological examination, including absence of nephrocalcinosis in the group of rats receiving 'high orthophosphate' within a period of 150 days, even though the weight of the kidneys was increased in this group.

Groups of 26-day old female albino rats were fed either a basal diet (control) or diets containing phosphoric acid, monosodium phosphate, disodium phosphate or trisodium phosphate at doses between 2,556 and 7,836 mg/kg bw (Mackay and Oliver, 1934). The rats were killed 44 days later. Addition of inorganic phosphate in any form led to increase of the kidney weights and gross examination revealed that kidneys were enlarged and firm with a pebbled surface produced by numerous scars in all dosed groups. Renal lesions in the form of cells necrosis of the convoluted tubules, regeneration of atypical epithelium and calcification of the necrotic debris were found in rats from all groups that had received phosphate in the diet while the kidneys from control animals were normal.

Female Wistar rats were fed a basal diet or a basal diet containing various concentrations of calcium, magnesium and phosphorus in the form of calcium oxide, magnesium oxide and monosodium phosphate (Chow et al., 1980). The experiments lasted for either 7 or 11 weeks. The concentrations of calcium and phosphorus were 0.4, 0.5, 0.8, 1.0, 1.5 and 2% of the diet dry matter (equivalent to 360,

450, 720, 900, 1,350 and 1,800 mg/kg bw per day) while the concentrations of magnesium were 0.2%, 0.4%, 0.8% and 1% of diet dry matter (equivalent to 180, 360, 720 and 900 mg/kg bw per day). The low levels of the minerals met or exceeded the requirements for rats. Magnesium phosphate uroliths developed in the renal pelvis, bladder and/or ureter of rats fed diets containing 1% magnesium (900 mg/kg bw per day) with either 1.0% or 0.5% phosphorus (900 or 720 mg/kg bw per day). Calcium phosphate uroliths formed in the renal tubules of the corticomedullary junction of rats fed a diet containing phosphorus ≥ 0.8% (720 mg/kg bw per day) and magnesium ≤ 0.8% of diet dry matter (≤ 720 mg/kg bw per day). The incidence and severity of the uroliths were reduced by increasing the magnesium content from 0.2 (180 mg/kg bw per day) to 0.8% (720 mg/kg bw per day) and by increasing the calcium to phosphorus ratio to > 1. The results indicated that interactions among the dietary content of calcium, magnesium and phosphorus affects incidence, severity and type of uroliths in rats.

Three-week-old female (RIV:TOX) rats were allowed to acclimate for 13 days on a diet containing 0.4% phosphorus and 0.04% Mg (Mars et al., 1988). Phosphorus was added in the form of monosodium phosphate dihydrate. The rats were transferred to four groups (6 animals per group) and fed diets varying in phosphorus and magnesium content only. These diets consisted of either 0.2% or 0.6% P and 0.02% or 0.04% Mg; another four groups were fed 0.4% or 0.8% P and 0.02% or 0.04% magnesium (the 0.2, 0.4, 0.6 and 0.8% P doses were calculated to 240, 480, 720 or 960 mg/kg bw per day, respectively (EFSA, 2012). The study lasted for 28 days. Groups fed a diet containing 0.4%, 0.6% and 0.8% P showed a statistically significant decrease in urinary calcium levels but faecal excretion was not systematically affected. Dietary content of 0.4%, 0.6% and 0.8% P increased faecal excretion of Mg ($p < 0.01$) and decreased urinary excretion of Mg ($p < 0.01$). Increased dietary P intake was positively correlated with urinary excretion of P ($r = 0.99$). Kidney weights were statistically significantly increased by dietary P ($p < 0.01$) and so were kidney levels of Ca ($p < 0.01$) and P ($p < 0.01$). Calcification was only investigated in the groups fed on a diet of 0.2% and 0.6% P. Calcification of the kidney was only found in the group receiving 0.6% (720 mg/kg bw per day) P and all the animals showed some degree of nephrocalcinosis in that group.

Ritskes-Hoitinga et al. (1989) studied the effects of a control diet containing 0.4% phosphorus (1.51 g monosodium phosphate dihydrate/100 g diet) and a diet containing 0.6% phosphorus (2.52 g monosodium phosphate dihydrate/100 g diet) (equivalent to approximately 480 and 720 mg/kg P bw per day) fed to female SPF-derived outbred Wistar rats for 28 days. The treatment with 0.6% phosphorus resulted in statistically significant increase in marked kidney calcification. In rats fed the 0.6% phosphorus diet, phosphorus retention and urinary excretion were greater compared with rats fed the 0.4% phosphorus diet. The following indicators of kidney function were examined: urinary volume, urine and plasma osmolality, urine and plasma creatinine, urine and plasma urea, urea and creatinine clearance and urinary albumin excretion. Of these indicators, only urinary albumin excretion was significantly increased in rats fed the diet containing 0.6% phosphorus. Urinary pH was also decreased in the group fed the high phosphorus diet. A statistically significant increase in calcium, phosphorus and magnesium content in the kidney was observed ($p < 0.01$, for all).

Body weight and feed intake was not affected. No no-observable-adverse-effect level (NOAEL) could be derived from this study.

Female Wistar rats were fed a diet of monopotassium phosphate in levels corresponding to either a normal phosphorus diet or high phosphorus diet (Matsuzaki et al., 2001). The content of monopotassium phosphate in normal phosphorus diet was 6,848 g/kg and 46,361 g/kg (corresponding to 822 and 5,563 mg/kg bw per day) in the high phosphorus diet. The experiment was ended after 21 days. A statistically significant increase in phosphorus intake was observed in animals in on the high phosphorus diet as well as a decrease in magnesium intake. Calcium, magnesium and phosphorus concentrations in the kidney were significantly increased and kidney dry weight was also increased in the group fed the high phosphorus diet compared with the group fed the normal phosphorus diet. Nephrocalcinosis was observed in all the rats fed on the high phosphorus diet and was not observed in the kidneys of the animals fed the normal phosphors diet. Serum urea nitrogen concentration as well as creatinine, albumin, *N*-acetyl-β-D-glucosaminidase activity and β2-microglobulin in urine were not affected. Calcium and magnesium concentration in urine showed a statistically significant decrease in the rats fed high phosphorus compared with rats fed normal phosphorus diet. The phosphorus content in urine was statistically significantly increased in the rats fed high phosphorus. Calcium absorption was unaffected whereas magnesium absorption was decreased and phosphorus absorption was increased in the high phosphorus group. The NOAEL of this study was 187 mg P/kg bw per day.

Dog

Male Beagle dogs were given equimolar amounts of dipotassium phosphate (trihydrate) or disodium phosphate (dihydrate) daily by gavage; the control group was given the vehicle (water) (Schneider et al., 1981. In the first week, the doses were 2,080 mg/kg bw per day dipotassium phosphate and 1,625 mg/kg bw per day disodium phosphate and the animals were dosed prior to their food. Because vomiting occurred the doses were halved, and food was given prior to the test solutions. In weeks 2–9, the animals received 1,040 mg/kg bw per day dipotassium phosphate and 812.5 mg/kg bw per day per day disodium phosphate. The doses in weeks 10–22 were as in the first week, i.e. 2,080 mg/kg bw per day dipotassium phosphate and 1,625 mg/kg bw per day disodium phosphate. At the end of the 9th week, two animals from each group were killed and the remaining animals were killed at the end of the 22nd week. The kidneys from all the animals were examined by light microscopy and kidneys from 2 animals in each group were examined by electron microscopy. Nephrocalcinosis with disseminated atrophy of the proximal tubule was found in animals treated with dipotassium phosphate or disodium phosphate and the changes were more marked after 22 weeks than after 9 weeks.

Diphosphate

Rat

Sprague–Dawley rats were administered tetrasodium diphosphate by oral gavage for 90 days (5 doses per week) according to OECD test guideline 408 (OECD, 1998) at doses of 250, 500 and 1,000 mg/kg bw per day (Seo et al., 2011). Control animals received filtered tap water only. There were no treatment-related deaths in any of the groups. The only clinical finding was hair loss in female rats at 500- and 1,000-mg/kg bw per day groups. Body weight gains were lower in males of the 1,000-mg/kg bw per day group compared with controls. Urinalysis results were normal for all groups. Total white blood cell counts were statistically significantly increased compared with controls in males and females of the highest dose group. In the 1,000-mg/kg bw per day group, neutrophil counts were statistically increased in females and lymphocyte counts statistically significantly decreased. Total red blood cell, haemoglobin, haematocrit, prothrombin time and activated partial thromboplastin time were statistically significantly reduced in males of the 1,000-mg/kg bw per day group compared with controls. Prothrombin time was also statistically significantly reduced in males of the 500-mg/kg bw per day group. Numerous changes to serum chemistry where also detected in treated animals. Serum total protein was statistically significantly reduced in males and females in the 500- and 1,000-mg/kg bw per day groups. Albumin was statistically significantly decreased in males of the 500- and 1,000-mg/kg bw per day groups. This reduction in albumin was also observed in females of the 1,000-mg/kg bw per day group. The albumin/globulin ratio was statistically significantly increased in the 500- and 1,000-mg/kg bw per day females, and the 1,000 mg/kg bw per day males. Serum aspartate aminotransferase (AST) was statistically significantly increased in high-dose males, and alanine aminotransferase (ALT) was statistically significantly decreased in high-dose females. Serum calcium (males and females $p < 0.01$), phosphorus (males $p < 0.01$; females $p < 0.05$), sodium (females only $p < 0.01$), potassium (males only $p < 0.05$) and chloride (males only $p < 0.05$) were statistically significantly reduced in the high-dose groups. Serum phosphate and sodium were also statistically significantly reduced in the 500-mg/kg bw per day males and females. In comparison to control values, relative (not absolute) liver weights in males of the 500- and 1,000-mg/kg bw per day groups were statistically significantly increased ($p < 0.05$). The absolute and relative liver weights of the 1,000-mg/kg bw per day females, and the relative liver weights of the 500- and 1,000-mg/kg bw per day females were statistically significantly increased (all $p < 0.01$). There were no gross pathological findings. The only histopathological findings were kidney lesions; cortical tubular basophilia of the renal tubule was more evident in males of the 1000-mg/kg bw per day group. Mineralisation of the kidney was also observed in females of the 1000-mg/kg bw per day group.

The authors of the study considered the findings regarding haematological parameters most likely not be toxicologically relevant and they concluded that the NOAEL for this study is 500 mg/kg bw per day tetrasodium diphosphate (corresponding to 116 mg/kg P bw per day).

The Panel agrees with this NOAEL for calcification and lesions of the kidney.

Tetrasodium diphosphate was administered to rats (10 animals/sex per group) via their diet at concentrations of 1.0%, 2.5% and 5% (approximately 900, 2,250 and 4,500 mg/kg bw per day) for 16 weeks (Datta et al., 1962) A control group received untreated diet only. After the end of treatment liver and kidney function tests as well as haematology, organ weights, macroscopic and microscopic examinations were conducted. There was no effect on liver function or haematology. However, the

kidney function (measured by specific gravity of urine between 8 and 24 h of water deprivation) of males in the 2.5% and 5% groups and females of the 5% group was impaired. Animals of the 5% group had statistically significant increases in relative weights of the heart, stomach ($p < 0.01$), intestines (females only; $p < 0.01$), kidneys (male: $p < 0.05$; females: $p < 0.01$) and testes ($p < 0.05$). The relative kidney weights were also statistically significantly increased ($p < 0.01$) in females of the 2.5% group. Macroscopic examinations revealed pale, pitted kidneys, calcification of kidneys, and hypertrophy and haemorrhages of the cardiac/pyloric border of stomach in male and female animals of the 5% group and females of the 2.5% group. The kidney was the only organ/tissue to show microscopic changes. At all doses, there was 95–100% of the group affected by microscopic changes, which were primarily in the cortex for the 1.0% and 2.5% groups. The main observations in the cortex were cortical atrophy and cortical hyaline degeneration, whereas the medullary zone was more affected in the rats treated with 5% tetrasodium diphosphate. The main findings in the medullary zone were medullary calcification and medullary necrosis. Tubular casts and chronic inflammatory changes were also observed in the 2.5 and 5% groups. Haemorrhages and exudates were observed in all groups in a dose-dependent manner. The Panel concluded that the NOAEL for this study was less than 1.0% (the lowest dose tested; approximately 900 mg/kg bw per day tetrasodium diphosphate). This corresponds to 209 mg/kg bw per day P assuming that the anhydrous form has been used.

Triphosphates

Rat

Rats (14 males/group) were administered 0.2%, 2% and 10% (equivalent to 180, 1,800 and 9,000 mg/kg bw per day) of sodium triphosphate (corresponding to pentasodium triphosphate) in diet for 28 days (Hodge, 1956). A control group receiving 9,000 mg/kg sodium chloride was also included. Three rats were sacrificed from each dose level on the 3rd, 7th and 14th day of the experiment and the remaining 5 rats on day 28. Early kidney changes compatible with phosphate nephritis were evident on the 3rd day in rats receiving 9,000 mg/kg bw per day sodium triphosphate, including nuclear pyknosis, coagulative necrosis and early breakdown of cells of the broad limb of Henle. These changes had become more pronounced by day 7, with tubular necrosis having spread from its origin near the junction of the outer zone of the medulla to the inner cortex. By day 14, the 9,000 mg/kg group had further severe changes in the tubules, including tubular necrosis with dilatation of the proximal convoluted tubules and subcapsular spaces of glomeruli. Clinical signs included growth retardation and increased kidney weight at the 9,000 mg/kg bw per day. Sodium chloride at 9,000 mg/kg bw per day also resulted in an increase in average kidney weight with dilated tubules and acute pyelitis. The rats that received 1,800 mg/kg triphosphate in diet had inflammatory changes in the kidney which were not characteristic of tubular necrosis as such but were likely to be due to the phosphate in the diet (as stated by the study authors). The animals administered 180 mg/kg bw per day had no test material-related kidney abnormalities. The Panel therefore concluded 180 mg/kg bw per day (corresponding to 45 mg/kg P bw per day) to be the NOAEL in this study.

Dog

Dogs (4 animals) were administered 100 mg/kg bw per day of sodium triphosphate (corresponding to pentasodium triphosphate) in diet for 28 days (Hodge, 1956). The tissues of the dogs receiving 100 mg/kg bw per day were normal, with no apparent histological changes. A second group of dogs (4 animals) were fed sodium triphosphate on a program of increasing dose, starting at 1,000 mg/kg and ending at 4,000 mg/kg 5 months later as follows: 1,000 mg/kg bw per day for 2 weeks, 1,500 mg/kg for 3.5 weeks, 2,000 mg/kg bw per day for 2.5 weeks, 2,500 mg/kg bw per day for 6.5 weeks, 3,000 mg/kg bw per day for 1 week, 3,500 mg/kg bw per day for 2 weeks and 4,000 mg/kg bw per day for 4 weeks. One dog began to lose weight on the 2,500 mg/kg bw per day dose, whereas the three other dogs only lost weight once on the 4,000 mg/kg bw per day diet. Blood samples were taken at the beginning and the end of the studies, which gave normal haematological values. Organ weights were normal. At necropsy, hypertrophy of the left ventricle and tubular damage in the kidney was evident in dogs receiving the high dose. The kidneys showed focal areas of granulomatous response with associated multinucleated giant cells. A NOAEL for this study is difficult to determine due to the varying dose that was administered, and necropsy was only performed at the end of the dosing period with the highest dose.

Polyphosphates

Rat

Rats (14 males/group) were administered 0.2%, 2% and 10% of sodium hexametaphosphate (corresponding to soluble sodium polyphosphate) in their diet for 28 days equivalent to 180, 1,800 and 9,000 mg/kg bw per day sodium hexametaphosphate, respectively (Hodge, 1956). Sodium triphosphate (corresponding to pentasodium triphosphate) was also tested in this study (see above under triphosphate). Since the results with sodium hexametaphosphate are identical with those found with sodium triphosphate with a NOAEL of 180 mg/kg bw per day (corresponding to 55 mg/kg P bw per day), no review of the results with hexametaphosphate is made here.

In a limited 28-day study, male weanling rats (5 animals/group) were given a diet supplemented with sodium hexametaphosphate at a concentration of 0.2%, 2%, 5% or 10% equivalent to 180, 1,800, 4,500 and 9,000 mg/kg bw per day sodium hexametaphosphate, respectively (Franklin Institute Research Laboratories, 1973). At sacrifice on days 3, 7, 15 and 28 relative splenomegaly was observed. The kidneys were pale and swollen and renal tubular necrosis was 'remarkable' (no information on the time points at which these observations were made). Following administration of a diet containing 2% sodium hexametaphosphate, acute pelvic inflammation was observed on day 28. There were no adverse effects following administration of a diet containing 0.2%, equivalent to 180 mg/kg bw per day sodium hexametaphosphate (corresponding to 55 mg/kg bw per day P) which was thus derived as the NOAEL.

Groups of Wistar rats (12 animals/group) were given a diet containing sodium hexametaphosphate at 0.93% and 3.5% for 50, 60 or 150 days equivalent to 837 and 3,150 mg/kg bw per day sodium hexametaphosphate, respectively (Dymsza et al., 1959). There were no adverse physiological effects observed in clinical tests (determination of haemoglobin and blood serum calcium and phosphorus content after 60 days, and red blood cell counts, haemoglobin, and blood serum calcium and phosphorus after 150 days), necropsies (organ weights after 60 days) or microscopic examinations (heart and kidney after 150 days) at either dose. The Panel concludes that due to the limited nature of this study it is difficult to derive a NOAEL.

Summary

In summary, results of multiple studies in rats and dogs ranging from 28 to 150 days have demonstrated that kidney is a target organ to phosphates at high doses. At high phosphate loads, excess phosphate causes increased bone demineralisation and release of calcium. This mechanism is part of a physiological regulatory mechanism leading to calcification of the kidney and tubular nephropathy.

The Panel noted that the highest reliable NOAEL for kidney effects, 500 mg/kg bw per day corresponding to 116 mg/kg bw per day phosphorus, was identified in a 90-day rat study with tetrasodium diphosphates performed according to OECD guidelines (Seo et al., 2011). In the same study, a dose of 1,000 mg/kg bw per day corresponding 233 mg/kg bw per day phosphorus was demonstrated to induce effects in the kidney.

3.5.6. Genotoxicity

Phosphoric acid, phosphates, diphosphates, triphosphates and polyphosphates have been tested for genotoxicity in a variety of *in vitro* and *in vivo* assays. In neither *in vitro* nor *in vivo* assays did any of the tested phosphates produce a positive response.

In vitro tests included *Salmonella* Typhimurium mutagenicity assay (unpublished report from Litton-Litton Bionetics cited in JECFA 1982b, Haworth et al., 1983; Cipollaro et al., 1986; Newell et al., 1974; Ishidate et al., 1984; Kim et al., 2010; Fujita and Sasaki, 1990), *Saccharomyces cerevisiae* mutagenicity assay (unpublished report from Litton Bionetics cited in JECFA 1982b), *Escherichia coli* mutagenicity assays (Demerec et al., 1951; Olivier and Marzin, 1987), chromosomal aberration test in Chinese hamster fibroblasts (Ishidate et al., 1984) and in human embryonic lung cells (unpublished report from Litton Bionetics cited in JECFA 1982b).

In vivo tests included chromosomal aberration test in rats (unpublished report from Litton Bionetics cited in JECFA 1982b), dominant lethal assay in rats (Newell et al., 1974), host-mediated assay in mice (Newell et al., 1974) and mouse translocation test (Newell et al., 1974).

There is one reported study where the authors claimed that phosphoric acid (E 338) increased the mean tail length and mean tail intensity in Comet assay in human lymphocytes *in vitro* (25, 50, 100,

200 μg/mL) (Yilmaz et al., 2014). However, the relevance of the findings reported in this study for risk assessment is questionable.

The Panel concluded that available data clearly show that phosphate is not genotoxic in standard test systems.

3.5.7. Chronic toxicity and carcinogenicity

There are few chronic toxicity or carcinogenicity studies available for the phosphates under evaluation. Only data on tetrasodium diphosphate, sodium triphosphate and sodium metaphosphate (also referred as sodium hexametaphosphate or Graham's salt) are available. Furthermore, the studies are relatively old, of variable quality and not performed according to current guidelines.

Diphosphates

Rat

Tetrasodium diphosphate was administered to groups of rats (24–36 animals/group; strain, age and numbers per sex not stated) in their diets at concentrations of 1.8%, 3% or 5% (approximately 810, 1,350 and 2,250 mg/kg bw per day) for 6 months (Hahn et al., 1958; Hahn and Seifen, 1959). Control animals received basic control diet. Nephrocalcinosis was observed in animals administered 1,350 or 2,250 mg/kg bw per day tetrasodium diphosphate. In the group at 1,620 mg/kg bw per day, a slight, but statistically significant increase in kidney weights was recorded and microscopic examination revealed renal calcification in some animals (number not stated). The study authors noted that slight renal calcification was also observed in the control animals but as stated by JECFA (1982b) was much less extensive than in the treated animals. No other adverse effects were reported. Therefore, the NOAEL under the conditions of this study can be concluded to be less than 810 mg/kg bw per day (corresponding to 189 mg/kg P bw per day) tetrasodium diphosphate in the diet. A lower concentration of 1.1% (approximately 495 mg/kg bw per day) of tetrasodium diphosphate was later tested under the same conditions for 6 months (Hahn, 1961; JECFA, 1982b). There was slight growth retardation initially, but this did not persist throughout the exposure period. After 39 weeks, slight kidney calcification was observed.

Triphosphates

Rat

Groups of weanling albino rats (50 animals/sex per group) were maintained on diets containing 0%, 0.05%, 0.5% and 5% (equivalent to 0, 25, 250 and 2,500 mg/kg bw per day) sodium triphosphate (corresponding to pentasodium triphosphate) for 2 years (Hodge, 1959). Body weights of the animals were recorded, blood samples taken, and urine analysis performed during the study. At the end of the experimental period, surviving rats were terminated and the tissues and organs fixed and sectioned and studied for histopathology. Bone samples were collected at termination to detect any abnormalities or calcification. At the 2,500 mg/kg dose, a clear growth depression was evident in male rats, which was less pronounced in female rats during both the first and second year. The mortality was high but the majority of the deaths (8–28 rats per group) were due to respiratory infection and pericarditis-peritonitis. The number of deaths from tumours was very small (≤ 2 animals per group) and did not differ between the different dose levels and controls, presenting no evidence for the carcinogenicity of sodium triphosphate. There was no indication of the treatment having an effect percentage of sugar and protein in urine. Haematology data indicated that male rats at the 1-year time point receiving the 2,500 mg/kg diet may have been slightly anaemic. The red blood cell count, haematocrit percentages and haemoglobin values were lower compared to other groups. A similar trend was not established for female animals. No other changes in haematological values were reported. In the high dose male rats, kidney weights, measured as the kidney to body ratio were higher than in other groups. A similar effect was also noted in the liver, brain, testes, stomach and heart weights. For female rats receiving the 2,500 mg/kg diet, an increase in liver and kidney weights was also seen in the 2,500 mg/kg group. Bone analysis revealed shorter femur length in both sexes receiving the 2,500 mg/kg diet, an indication that the rats had failed to grow as stated by study authors. All calcium–phosphorus bone ratios were reported to be within normal range. At the end of the 2-year study period, the surviving animals were sacrificed, and tissues gathered for histological examination. The main finding was enlarged, granular kidneys in rats of both sexes receiving the 2,500 mg/kg diet. Convoluted renal tubules were found to be dilated, especially in the loop of Henle. Hyaline casts were present in most cases. Associated changes were interstitial fibrosis and hyalinised,

fibrotic glomeruli. The collective term to describe the condition was 'chronic tubular nephropathy', which was present in all rats receiving the high dose. However, control rats, and rats receiving 25 mg/kg bw per day and 250 mg/kg bw per day showed similar changes and therefore establishing definitive treatment-related causality was not possible. Furthermore, chronic pyelonephritis is stated by the study authors to be frequently present in older rats. However, the study authors conclude that the chronic tubular nephropathy appears to be phosphate-specific in the high dose group due to scarcity of inflammatory cell infiltrate, gross enlargement of the kidneys, extreme dilation of tubules of loop of Henle and calcification. Tumour incidence in the control and treatment groups was comparable and not considered to be treatment related. Based on the test article-specific kidney effects which were seen only at the high dose. The panel concluded that 250 mg/kg bw per day (corresponding to 63 mg/kg P bw per day) was the NOAEL in this study.

Polyphosphates

Rat

The carcinogenicity of sodium metaphosphate (corresponding to soluble sodium polyphosphate) was investigated in F344 rats (50 animals/sex per dose; 6 weeks old) (Kitahori et al., 1998). Sodium metaphosphate was administered in the diet at concentrations of 1.5% or 3.0%. (approximately 750 and 1,500 mg/kg bw per day) for 108 weeks. There was also a control group that received untreated diet. Blood samples were taken from all surviving animals in week 108 for haematology and clinical chemistry investigations. Urinalysis was also conducted. Macroscopic and microscopic examinations were conducted on all animals in the study. There were no treatment-related effects on survival, body weight gains, haematology, clinical chemistry or urinalysis. Many tumours developed in all groups, including the controls. However, the organ distribution and histological characteristics were comparable to those reported to occur spontaneously in this strain of rat. The authors of the study concluded that sodium metaphosphate does not induce tumours in rats, when given orally in the diet for 108 weeks. With regard to non-neoplastic effects, mineralisation (marked calcium deposition in the pars intermedia of the kidney in the 3% group), cast formation and basophilic tubular cell proliferation was observed in the kidneys of the treated female animals. The panel concluded that the NOAEL for carcinogenicity in this study was 1,500 mg/kg bw per day (corresponding to 456 mg/kg P bw per day), the highest dose tested whereas the NOAEL for microscopic effects observed in the kidneys was < 750 mg/kg bw per day (corresponding to 229 mg/kg P bw per day).

Groups of albino Rochester rats (50 animals/sex per group; described as weanling) were administered a diet containing 0.05%, 0.5% and 5% sodium hexametaphosphate (corresponding to soluble sodium polyphosphate) (approximately 25, 250 and 2,500 mg/kg bw per day) for 2 years (Hodge, 1960). Body weights were recorded weekly for the first 3 months and then every 2 weeks thereafter. Blood samples were taken from 5 animals/sex once before treatment began, monthly for the first 6 months, every 2 months for the rest of the first year, and then every 3 months for the second year. Haemoglobin values, red blood cell characteristics, red blood cell counts, white blood cell counts and differential counts were recorded for all blood samples. Pooled urine samples were collected three times per year to determine sugar and protein content. At termination, tissues and organs from 10 animals/sex per group were collected and studied microscopically. Mortality rates were high (64–78%) and were primarily due to respiratory infections. Tumour incidence increased with age in almost all groups, but there was no dose relationship with sodium hexametaphosphate. Kidney weights were increased in animals in the 5% group and microscopic examinations revealed increased calcification in the tubules of the kidneys. The authors of the study stated that the calcification is believed to be an intensification of the severity of naturally occurring processes of infection and degeneration. However, some of the rats in the 5% group had normal kidneys. Therefore, the NOAEL in this study is approximately 250 mg/kg bw per day (corresponding to 76 mg/kg P bw per day) hexametaphosphate based on treatment-related effects on the kidney and reduced body weight gain. There was no evidence of increased tumour incidence in any group.

Graham's salt (sodium hexametaphosphate) was administered to groups of rats (24–36 animals/group; strain, age and numbers per sex not stated) in their diets at concentrations of 1.8%, 3% or 5% (approximately 1,620, 2,700 and 4,500 mg/kg bw per day) for 6 months (Hahn et al., 1958; Hahn and Seifen, 1959). Control animals received untreated diets. In the 3% and 5% groups, body weight gain was statistically significantly reduced (p value not stated). In the 3% group, the reduction was transient, whereas in the 5% group the reduction persisted through the 6-month exposure period. No such effect on body weight gain was observed in the 1.8% group. Nephrocalcinosis was observed in

animals administered 3% or 5% sodium hexametaphosphate. The renal calcification was less marked in animals treated with Graham's salt than with other phosphates, such as sodium tripolyphosphate. No other adverse effects were reported.

In summary, there are three 2-year carcinogenicity studies in rats available, one with sodium triphosphate and two with sodium polyphosphate. In none of the studies were there any relationship between treatment with the phosphates and tumour development. The Panel thus concluded that phosphates do not have any carcinogenic potential. The key adverse effects in these three life time studies as well as in two chronic toxicity studies of 6 months duration were calcification in the kidneys and tubular nephropathy. The lowest tested level of phosphate causing an effect in the kidney was approximatively 750 mg/kg bw (corresponding to 229 mg P/kg bw per day) in a 2-year study with sodium metaphosphate (Kitahori et al., 1998). Two reliable NOAELs could be identified, 250 mg/kg bw per day (corresponding to 63 mg/kg P bw per day) and 250 mg/kg bw per day (corresponding to 76 mg/kg P bw per day) with sodium triphosphate and sodium hexametaphosphate, respectively (Hodge, 1959, 1960).

In conclusion, the only significant adverse effect of phosphates in standard short-term, subchronic and chronic toxicity studies is calcification of the kidney and tubular nephropathy. These kidney effects are observed in all species investigated and the onset of the effects are apparently quite rapid with marked effects seen already after a few weeks of treatment.

3.5.8. Reproductive and developmental toxicity

Phosphoric acid, calcium and magnesium phosphate

Mouse

Female albino CD-1 outbred mice (23–26 mated animals/group) were administered monocalcium phosphate monohydrate (corresponding to calcium dihydrogen phosphate) by gavage in doses of 0, 4.65, 21.6, 100 or 465 mg/kg bw per day through gestation days (GD) 6–15. All animals were observed daily for appearance and behaviour, and body weights were recorded on GD 0, 6, 11, 15 and 17. On GD 17, all dams were subjected to caesarean section and the number of implantation sites, resorption sites and live and dead fetuses were documented. The body weight of the live fetuses was measured. All fetuses were examined for the presence of external congenital abnormalities. Furthermore, one-third of the fetuses were examined for visceral abnormalities and the remaining two-thirds for skeletal abnormalities. Treatment with monocalcium phosphate monophosphate induced no maternal toxicity or developmental effects at dose levels up to 465 mg/kg bw per day in mice, the highest dose tested (FDRL 1974, cited in (JECFA, 1982b)].

Rat

In a study with rats given 0.4% or 0.75% (equivalent to 200 or 375 mg/kg bw per day) dietary phosphoric acid over the whole life span and with successive generations no adverse effect on the growth of three successive generations was observed. The animals were mated when they were 32-week-old as well as 11 weeks later (only the 0.4% group); no adverse effects were noted as evaluated by the body weight of the dams, the number of living pups and stillborn per litter, the average pup weight at birth and the number of pups at weaning. No significant differences were noted in haematological parameters in comparison with control rats. The histological examination (liver, spleen, adrenals, testes, skeletal muscle, femur and kidney) revealed no pathological changes. Teeth were examined in a number of rats following dietary administration for 3–16 months (both 0.4% and 0.75% groups); no extensive lesions were observed except for dental attrition of the molars which was slightly more marked in the treated group compared to the control group. According to the authors the dental attrition was not to be regarded as a harmful effect (Bonting and Jansen, 1956).

Female albino rats (Wistar derived stock) (25–29 mated animals per group) were administered monocalcium phosphate monohydrate by gavage (vehicle: water) at doses of 0, 4.1, 19.1, 88.5 or 410 mg/kg bw per day through GD 6–15. All animals were observed daily for appearance and behaviour, and body weights were recorded on GD 0, 6, 11, 15 and 20. On GD 20, all dams were subjected to caesarean section and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of live pups were recorded and all fetuses were examined grossly for the presence of external abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations and the remaining two-thirds were examined for skeletal defects. Treatment with monocalcium phosphate monophosphate induced no maternal toxicity or

developmental effects at dose levels up to 415 mg/kg bw per day in rats, the highest dose tested (FDRL 1974, cited in (JECFA, 1982b)).

Three groups (groups I–III) of pregnant Wistar rats (10 weeks old) were treated during GD 0–20 either with the standard diet (group I), corn oil vehicle on standard diet (group II) or on standard diet supplemented with 175 mg/kg bw per day tricalcium phosphate (group III) (Güngörmüş et al., 2010). In a second study, the dose was 350 mg/kg bw per day (Kiliç et al., 2012). Vehicle and tricalcium phosphate were administered orally by gavage. Caesarean section was performed on GD 20. No signs of illness or abnormal behaviour were observed in the dams during the treatment. There were no statistically significant effects on fetal mortality, fetal body lengths and weights. No resorptions, short or absent tail, fore or hind limbs were observed in this study. The placental weights, but not placental index (weight of placenta/weight of fetus), of the tricalcium phosphate group (Group III) were found to be statistically decreased compared to group I (standard diet) ($p \leq 0.05$). At skeletal examination, there were no gross skeletal anomalies, incomplete ossification, reduced sternebrae number, misshaped sternebrae, rib or other bones. Moreover, the ossification in fore- and hind-limbs, sacral and caudal bones was complete, there were no extra or missing bones observed in any of the groups. According to morphometric measurements of fetuses, the following parameters were significantly decreased; lengths of left ulna (28.3%, $p \leq 0.05$), right femur (29.8%, $p \leq 0.05$), left femur (34.9%, $p \leq 0.05$) and diameter of the skull of y-axis (12.3%, $p \leq 0.05$) in the tricalcium phosphate treatment groups when compared with control (group I). However, only ulna and left femur were statistically significant different from the vehicle control (group II, $p \leq 0.05$). Fetal body lengths and weights were not affected by treatment. Furthermore, there was an increase in transumbilical diameter in the treatment group (group III) both compared to the control (group I) ($p \leq 0.05$) and oil control groups (Group II) ($p \leq 0.05$) (Güngörmüş et al., 2010).

The study from Güngörmüş et al. (2010) has, however, several shortcomings and inconclusive results. There were only five pregnant rats per group in the study which had two control groups, but only one dose group. The number of fetuses is 11 in the untreated control group, 6.6 in the control group fed with vehicle and 10.5 in the calcium phosphate groups indicating poor performance of the study. Inconsistencies were observed between the results section where the authors conclude *'no gross structural anomalies or malformations'* and in the discussion where the sentence is found 'We observed several foetuses with malformations such as: reduced skull development and shorter forelimb and hindlimb formation'. The findings of a reduction in length of left ulna and bilateral femurs are thus most probably artefacts.

In the second study (Kiliç et al., 2010), histopathological changes in maternal liver, kidney, heart, brain, placenta and fetal liver and kidney were reported. In the fetuses, the absolute liver weight increased whereas the relative liver weight decreased which is inconsistent.

Given the inconsistencies and the uncertainty about the causing agent, the Panel considered the studies as inappropriate for risk assessment.

Rabbit

Virgin adult Dutch-belted female rabbits (15–27 artificially inseminated animals per group) were administered with monocalcium phosphate monohydrate by gavage (vehicle: water) at doses of 0, 2.17, 10.10, 46.7 or 217.0 mg/kg bw per day through GD 6–18. All animals were observed daily for appearance and behaviour, and body weights were recorded on GD 0, 6, 12, 18 and 29. On GD 29, all dams were subjected to caesarean section and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of live fetuses were recorded and all fetuses were examined grossly for the presence of external congenital abnormalities. Live fetuses were then placed in an incubator for 24 h for an evaluation of neonatal survival. All pups were then sacrificed and examined for visceral abnormalities and skeletal defects. Treatment with monocalcium phosphate monophosphate induced no maternal toxicity or developmental effects at dose levels up to 217 mg/kg bw per day in rabbits, the highest dose tested (FDRL 1974, cited in (JECFA, 1982b)).

Sodium and potassium phosphate

Mouse

Female albino CD-1 outbred mice (19–22 pregnant animals per group) were administered with monosodium phosphate by gavage at doses of 0, 3.7, 17.2, 79.7 or 370.0 mg/kg bw per day from GD 6 to 15. The vehicle used was water. Body weights were recorded on GD 0, 6, 11, 15 and 17. All

animals were observed daily for appearance and behaviour. On GD 17, all dams were subjected to caesarean section and the sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weight of the live pups was also measured. All fetuses were examined grossly for the presence of external congenital abnormalities. Furthermore, one-third of the fetuses were examined for visceral abnormalities and the remaining two-thirds for skeletal defects. No maternal toxicity or developmental effects were noted at dose levels up to 370 mg/kg bw, the highest dose tested (FDRL 1975, cited in (JECFA, 1982b)).

Groups of pregnant albino CD-1 mice were dosed by gavage with monopotassium phosphate from GD 6 through 16. Body weights were recorded on GD 0, 6, 11, 15 and 17 of gestation. On GD 17, all dams were subjected to caesarean section and the number of implantation sites, resorption sites and live and dead fetuses were recorded. The body weight of the live fetuses was also measured. All fetuses were examined for the presence of external congenital abnormalities. Furthermore, one-third of the foetuses were examined for visceral abnormalities and the remaining two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted for monopotassium phosphate at dose levels up to 320 mg/kg bw (FDRL 1975, cited in (JECFA, 1982b)).

Rat

Groups of 20 pregnant albino Wistar derived rats were dosed by gavage with monosodium phosphate (anhydrous) at dose level of 0, 4.1, 19.0, 88.3 or 410.0 mg/kg bw per day from GD 6 to 15. The vehicle used was water. Body weights were recorded on days 0, 6, 11, 15 and 20 of gestation. All animals were observed daily for appearance and behaviour. On GD 20, all dams were subjected to caesarean section and the sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weight of the live pups was also measured. The urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for the presence of external congenital abnormalities. Furthermore, one-third of the foetuses were examined for visceral abnormalities and the remaining two-thirds for skeletal defects. No maternal toxicity or developmental effects were noted at dose levels up to 410 mg/kg bw, the highest dose tested (FDRL 1975, cited in (JECFA, 1982b)).

Diphosphates

Mouse

Female albino CD-1 mice (25 mated animals/group) were administered from GD 6 to 15 with 0, 3.35, 15.6, 72.3 or 335 mg/kg bw per day disodium diphosphate by oral gavage (FDRL 1973, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 11, 15 and 17, and all animals were observed for clinical signs of toxicity. Food consumption was also measured. On GD 17, a caesarean section was conducted on all dams. The number of implantation sites, resorption sites, and live and dead fetuses was recorded. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the fetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 335 mg/kg bw, the highest dose tested.

Female albino CD-1 mice (25 mated animals/group) were with administered 0, 1.3, 6.0, 28 or 130 mg/kg bw per day tetrasodium diphosphate by gavage from GD 6 to 15 (FDRL 1975, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 11, 15 and 17, and all animals were observed for clinical signs of toxicity. Food consumption was also measured. On gestation day 17 a caesarean section was conducted on all dams. The sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses was recorded. The body weights of the live fetuses were recorded. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the fetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 130 mg/kg bw, the highest dose tested.

Hamster

Female golden hamsters (25 mated animals/group) were administered with 0, 1.66, 7.71, 35.8 or 166 mg/kg bw per day disodium diphosphate by gavage from GD 6 to 10 (FDRL 1973, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 8, 10 and 14, and all animals were observed for clinical signs of toxicity. On GD 14 a caesarean section was conducted on all dams. The number of implantation sites, resorption sites, and live and dead foetuses was recorded. The body weights of the live fetuses were measured. All fetuses were examined macroscopically for external

congenital abnormalities. One-third of the fetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 166 mg/kg bw, the highest dose tested.

Rat

Female albino Wistar-derived rats (25 mated animals/group) were administered with 0, 1.69, 9.24, 42.95 or 169 mg/kg bw per day disodium diphosphate by gavage from GD 6 to 15 (FDRL 1973, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 11, 15 and 20, and all animals were observed for clinical signs of toxicity. Food consumption was also measured. On GD 20 a caesarean section was conducted on all dams. The number of implantation sites, resorption sites, and live and dead fetuses recorded. The body weights of the live fetuses were measured. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the fetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 169 mg/kg bw, the highest dose tested.

Female albino Wistar-derived rats (25 mated animals/group) were administered with 0, 1.38, 6.41, 29.7 or 138 mg/kg bw per day tetrasodium diphosphate by gavage from GD 6 to 15 (FDRL 1975, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 11, 15 and 20, and all animals were observed for clinical signs of toxicity. Food consumption was also measured. On GD 20 a caesarean section was conducted on all dams. The sex, numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live fetuses were measured. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the foetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 138 mg/kg bw, the highest dose tested.

Rabbit

Female Dutch-belted rabbits (15 artificially inseminated animals/group) were artificially inseminated (were administered with 0, 1.28, 5.95, 27.6 or 128 mg/kg bw per day disodium diphosphate by gavage from GD 6 to 18 (FDRL 1973, cited in (JECFA, 1982b)). Maternal body weights were measured on GD 0, 6, 12, 18 and 29, and all animals were observed for clinical signs of toxicity. Food consumption was also measured. On GD 29 a caesarean section was conducted on all dams. The number of corpora lutea, implantation sites, resorption sites, and live and dead foetuses was recorded. The body weights of the live fetuses were measured. All foetuses were examined macroscopically for external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 h to evaluate neonatal survival. All surviving pups were sacrificed and examined for visceral and skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 128 mg/kg bw, the highest dose tested.

Triphosphates

Rat

A study previously described by Hodge (1959) combined a chronic toxicity and a reproductive study in rat. The reproductive study was carried out with the 250 mg/kg dose group and the control group. Sixteen females and 8 males were mated. They were mated again at 10 days after weaning of the first litter. Thereafter, 16 females and 8 males were selected from the control and 250 mg/kg group at weaning and continued on their respective diets. When the animals were 100 days old they were mated and they were thereafter mated again 10 days after weaning the first litter, and the whole procedure was repeated with the rats to produce a second litter of the third generation. Parameters of reproductive behaviour which were evaluated included number of females mated, number of pregnancies, mortalities and number of live births, organ weights and pathology. When 21 days old, 10 males and 10 females from each group were necropsied, and the test material-related abnormalities recorded. The initial mating (first generation, first litter) resulted in 14 pregnancies in the control group and 15 pregnancies in the test group receiving 250 mg/kg sodium triphosphate. No differences in performance were noted between the control and test animals. The second mating (first generation, second litter) resulted in 12 pregnancies in both test and control groups. No significant difference was reported between rats receiving the 250 mg/kg diet and the control rats. The first generation rats were raised to reach 100 days. They were then mated to produce the first litter of the second generation. By performance, the test and control rats were identical. The first litter of the second generation resulted in 12 pregnancies, with no difference in reproductive performance between

test and control rats. Similarly, the second litter of the second generation was raised with no complications or difference in survival, growth and fertility. The rats were raised to 100 days of age and mated. The first or second litter of the third generation were not affected in treatment-related effects when test and control rats were compared. All animals investigated revealed no remarkable pathological findings at necropsy, with no abnormalities in tissues of young animals. The authors of the study concluded that there was no evidence of reproductive toxicity associated with administration of 250 mg/kg sodium triphosphate. The report is lacking in detail, but it adds weight of evidence to the lack of reproductive and developmental effects of the triphosphates.

Rabbit

Dutch-belted rabbits (17 to 20 females artificially inseminated animals/group) were dosed by gavage with 0, 2.5, 11.6, 54 or 250 mg/kg sodium triphosphate (corresponding to pentasodium triphosphate) from GD 6 to 18 (FDRL 1973, cited in (JECFA, 1982b)). Between 13 and 16 mated rabbits became pregnant out of the 17 to 20 animals per group. Body weights were recorded on GD 0, 6, 12, 18 and 29. Clinical signs, behaviour and food consumption were monitored throughout the study. On GD 29, the animals were subjected to caesarean section and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. External abnormalities assessed and body weights were recorded. The live fetuses were maintained in an incubator and observed for neonatal survival for 24 h, after which surviving pups sacrificed and examined for visceral abnormalities and skeletal defects. No maternal toxicity or developmental effects were noted at dose levels up to 250 mg/kg bw, the highest dose tested.

Polyphosphates

Mouse

Female albino CD-1 mice (25 mated animals/group) were administered with 0 3.7, 17.2, 79.7 or 370 mg/kg bw per day sodium hexametaphosphate (corresponding to soluble sodium polyphosphate) by gavage from GD 6 to 15 (FDRL, 1974). Maternal body weights were measured on GD 0, 6, 11, 15 and 17, and all animals were observed daily for clinical signs of toxicity. Food consumption was also measured. On GD 17 a caesarean section was conducted on all dams. The sex, number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live fetuses were recorded. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the fetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 370 mg/kg bw, the highest dose tested.

Rat

Groups of albino Rochester rats (50 weanling animals/sex/group) were administered a diet containing 0.05%, 0.5% and 5% (equal to 26, 260 and 2,600 mg/kg bw per day), sodium hexametaphosphate for 2 years (Hodge, 1960). Animals (16 females and 8 males, 100 days old) from the 0.5% hexametaphosphate group and the untreated control group were selected for a reproductive toxicity study (P1 generation). These animals were bred to produce three F1 generations (F1a, F1b and F1c). The F1a generation were sacrificed on postnatal day 30. Adults from the F1b generation (P2) were mated at 100 days of age to produce the F2a generation, which was sacrificed on postnatal day 30. A second mating of the P2 animals produced the F2b generation, which at 100 days of age (P3) were mated to produce the F3a and F3b generations. The F3a animals were sacrificed on postnatal day 30. The F3b animals were sacrificed on postnatal day 21 and a microscopic examination conducted. Diet containing hexametaphosphate at a concentration of 0.5% and the control diet were available to the animals throughout the study depending on the test group. The study authors concluded that the average number of pups per litter was comparable between the control and treated groups, as was pup mortality, and pup organ weights (F3b only). The microscopic examination did not reveal any abnormal findings in treated animals. Therefore, there were no adverse effects observed under the conditions of this non-standard study. Although this is a non-standard study conducted pre-Good Laboratory Practice (GLP), in the absence of other more reliable studies it provides some reassurance that sodium polyphosphate, and other polyphosphates, do not have an adverse effect on reproduction up to a dose of approximately 260 mg/kg bw per day.

Female albino Wistar-derived rats (25 mated animals/group) were administered with 0, 2.4, 11.1, 51.7 or 240 mg/kg bw per day sodium hexametaphosphate by gavage from GD 6 to 15 (FDRL, 1974). Maternal body weights were measured on GD 0, 6, 11, 15 and 20, and all animals were observed daily

for clinical signs of toxicity. Food consumption was also measured. On GD 20 a caesarean section was conducted on all dams. The sex, number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were measured. The urogenital tract of each dam was also examined. All fetuses were examined macroscopically for external congenital abnormalities. One-third of the foetuses were examined for visceral abnormalities and two-thirds for skeletal abnormalities. No maternal toxicity or developmental effects were noted at dose levels up to 240 mg/kg bw, the highest dose tested.

Summary

In summary, there are a number of studies, although generally not conducted to current OECD guidelines, evaluating reproductive and developmental toxicity of the phosphates under evaluation. In studies performed in mice, rats, rabbits or hamsters, there are no signs of reproductive or developmental toxicity at any dose tested. The Panel thus concluded that exposure to phosphates do not present any risk for reproductive or developmental toxicity.

3.5.9. Other animal and *in vitro* studies

There are a large number of experimental *in vivo* and *in vitro* studies, many of which are quite recent, investigating the association of phosphates at high concentrations with pathologies other than kidney calcification and tubular nephropathy (Razzaque, 2012; Uribarri and Calvo, 2018).

Generally, *in vitro* systems, genetically modified animals and other animal models are used in these studies. It was difficult to establish underlining mechanisms and dose response for the observed effects. Nevertheless, findings in some of the studies (e.g. activation of metabolic pathways that promote cell transformation and cancer, regulation of osteopontin, induction of endothelial dysfunction, alterations of FGF-23 levels and the Wnt pathway balance, etc.) may indicate potential adverse effects of phosphates.

The Panel did not consider these sufficiently robust nor validated to be used in the risk assessment of phosphate as food additives.

Bone

Several studies in animals report that high phosphorus intake causes bone reabsorption or decreased bone formation.

Effect of high phosphorus intake on bone metabolism-related gene expression was demonstrated young and aged mice measuring PTH and mediators of osteoclastic bone resorption. Young (12 week old) and aged (80 week old) male mice (12 animals/group) were fed with control diet (0.3% P) or high P content diet (1.2% P) for 4 weeks. The high P content diet increased serum PTH in both young and aged mice and increased receptor activator of NF-kB ligand (RANK)/osteoprotegerin (OPG)mRNA ratio in the femur of aged mice (Katsumata et al., 2014).

Male Wistar rats (20 animals/group) were fed with control diet (0.6% phosphate) or high phosphate diet (1.2%) for 8 weeks. Bone mineral density (BMD) of femur and lumbar spine was investigated and high-phosphate intake diet did not appear to negatively impact BMD value (Huttunen et al., 2006).

Abnormal bone mineralisation occurred also when rats were given phosphoric-acid containing soft drinks instead of water. Young adult (30 days) and immature (30 days) Sprague–Dawley male rats (14 animals/group) has access to tap water (control) or cola-containing drink ad libitum for one week. Both adult and immature animals receiving cola-containing drink developed hypercalciuria and hyperphosphaturia. Immature rats developed significant reduction in calcium regulatory hormones such as $1\alpha,25(OH)_2D_3$ and $25\text{-}OHD_3$ but only adult rats showed developed significant hyperparathyroidism (Amato et al., 1998).

Four groups (9 animals/group) of male Wistar rats (5 week old) were fed with semi-purified diet non-supplemented or supplemented with 1%, 1.4%, or 2,2% calcium hydrogen phosphate (Hardwick et al., 1987). Rats receiving diet supplemented with calcium hydrogen phosphate did not show effect on whole blood or plasma ionised Ca, plasma, total Ca, or plasma inorganic P levels. Femur dry weight and length was not affected by the different diets, nor did bone Ca content increase with supplementation.

Anderson et al. (1977), investigated the effect of diets supplied by high phosphorus in monkeys. Nineteen (male and female) juvenile cinnamon ringtail monkeys were fed diets with Ca:P ratio of 1:4, 1:2.1, 1:0.4, 1:0.5 (corresponding to 1.20%, 2%, 0.40% and 0.47% P) up to approximately 7 years.

The results did not show any short or long-term effect in the skeleton in both young growing and adult monkey. The authors reported that those results are in contrast to studies in other species although the Ca:P tested were very similar.

The Panel concluded that effects observed on bone metabolism and bone mineralisation in animals are not well characterised enough to derive an association with dietary high phosphate intake.

3.6. Epidemiology on cardiovascular diseases

3.6.1. Studies on dietary phosphorus and cardiovascular diseases-related outcomes

Cardiovascular mortality

Chang et al. (2014) conducted a cohort study among healthy US subjects aged 20–80 years (NHANES III; 1998–1994, n = 12,366) to investigate the association between phosphorus intake and all-cause mortality and cardiovascular-specific mortality. Among those initially enrolled, 2,680 subjects were excluded from the analysis because of the presence of diabetes, self-reported history of myocardial infarction and/or congestive heart failure (HF) and/or stroke and/or cancer as well as subjects with extreme energy intakes and with eGFR of 60 mL/min*1.73 m^2 or lower. Out of the 12,366 initially enrolled individuals, 9,686 subjects were included in the analysis. Vital stats and cause of death was obtained by using The NHANES III mortality file from the study participation to 31 December 2006 (median follow-up time: 14.7 years, Interquartile Range (IQR): 13.1–16.2 years). Dietary intake data was assessed by a 24-h dietary recall. The median phosphorus intake was 1,166 mg/day (IQR: 823–1,610 mg/day); median phosphorus density was 0.58 mg/kcal (0.48–0.70 mg/kcal). Median values of phosphorus consumption in the lowest to highest quartiles were 629, 993, 1,356 and 1,992 mg/day, respectively. Estimated glomerular filtration rate values (mL/min*1.73 m^2) in the first, second, third and fourth quartile were as following: 102.6 SD = 0.7; 101.6, SD = 0.7; 102.1, SD = 0.6, 104.4, SD = 0.6. In the multivariate analysis, adjusted for age, sex, race, ethnicity, poverty income ratio, BMI, blood pressure (BP), smoking, physical activity, cholesterol, urine albumin/creatinine ratio, glomerular filtration rate and vitamin D, high absolute phosphorus intake (1,400 mg/day or more) was associated with high overall mortality (HR: 1.89, 95% confidence intervals (CI): (1.03–3.46) while phosphorus density was not (HR: 1.05; 95% CI: 1.01–1.10). For cardiovascular mortality neither absolute intake of phosphorus (HR: 1.02, 95% CI: 0.29–3.58) or phosphorus density (HR: 1.02, 95% CI: 0.93–1.12) were associated with an increased risk. When serum phosphorus was introduced in the models, the risk estimates for both absolute and density phosphorus intake and overall mortality did not change. Serum phosphorus was associated with overall mortality (HR: 1.37, 95% CI: 1.13, 1.67) per each 1 mg/dL increase in serum phosphorus (p = 0.002). The strength of the study was the long follow-up, the size of the study and the good control of confounding factors. The main limitation of the study was the use of a single 24-h recall assessing dietary intake, in particular, phosphorus intake. A single day is unlikely to be representative of usual individual intake, especially for phosphorus. The number of days necessary for assessing nutrients and energy intake seems to be at least 5 days. Non-differential misclassification error leads to HR biases towards the null.

Blood pressure

Alonso et al. (2010) investigated in two US multicentre cohort studies the association between phosphorus intake and hypertension. The study population consisted in 8,208 subjects (age range 45–65 years) from the Atherosclerosis Risk in Communities Study (ARIC) and 2,901 subjects (age range 45–84 years) from the Multi-Ethnic study of Atherosclerosis (MESA). Subjects with hypertension at baseline and with prevalent CVDs and diabetes were excluded from the analysis. Subjects with missing data were also excluded. Demographic, clinical and dietary data were collected at baseline. Dietary habits were assessed using a 66-item FFQ in the ARIC study and a 120-item FFQ in the MESA study. Three measurements were averaged to estimate systolic and diastolic BP. After an average follow-up of 7.1 years in the ARIC study and 3.8 years in the MESA study, 2,400 and 945 cases of hypertension were identified. The average phosphorus intake was 1,084 mg daily in the ARIC study and 1,103 mg daily in the MESA study. In the multivariate analysis, controlling for age, race, sex BMI, waist circumference, eGFR, education, income, physical activity, cigarette smoking, study site, alcohol intake, energy intake, calcium, vitamin D (only in ARIC), sodium, potassium, magnesium, fruits and vegetables and whole grains intake, no increased risk was found for phosphorus intake and hypertension in the pooled analysis of the two studies (HR: 1.01, 95% CI: 0.82–1.23). When the

analysis was conducted separately, no increased risk was found for both ARIC study (Q5, 1,472 mg phosphorus; HR: 0.97, 95% CI: 0.77–1.24) and MESA study (Q5, 1,526 mg phosphorus; HR: 1.10, 95% CI: 0.75; 1.61). The strength of the study was the pooled analysis of two cohort studies and the good control for confounding factors. The limitation of the study was the high number of excluded subjects mainly because of missing data, the lack of data comparing, for some important characteristics the study base and the subjects included in the study (selection bias).

Mazidi et al. (2017) conducted a cross-sectional study in Iran to investigate the association between diet, in particular phosphorus intake, and BP in individuals aged 35–64 years. Subjects with history of unstable angina, myocardial infarction, stroke, HF, peripheral vascular disease including transient ischaemic attack or amaurosis fugax, cardiovascular interventions or surgery, cancer, autoimmune, infectious and inflammatory diseases were excluded from the analysis. Participants were in total 5,670 subjects (2,179 males, mean age 50.1 years, SD = 8.1) and 3,491 females (mean age 48.2 years, SD = 7.8). Demographic information, clinical, anthropometric (weight, height, waist circumference) and dietary data (24-h recall) were collected for all participants. Weight and height, total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were also measured. A significant inverse correlation between phosphorus intake and systolic BP ($p = 0.04$) and diastolic BP ($p = 0.03$) was found. The limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality and the lack of a proper statistical method.

Left ventricular mass

Yamamoto et al. (2013), within the MESA, investigated, using a cross-sectional design, the association between dietary phosphorus with left ventricular mass (LVM) in 4,494 subjects free of known CVD (mean age 61.6 years) and with completed dietary data. Demographic, clinical and lifestyle data were collected at baseline. Dietary phosphorus intake was assessed by a 120-item FFQ. Mean dietary phosphorus intake was 1,167 mg/day in men and 1,017 mg/day in women. The mean and standard deviation LVM for men and women were 168.6 ± 36.8 g and 123.8 ± 27.4 g, respectively. In the multivariate analysis, after controlling for age, race, height and weight, total dietary calories, dietary sodium, smoking, alcohol use, education, moderate-vigorous physical activity, diabetes status, systolic BP, antihypertensive medication use, urinary albumin to creatinine ratio, C-reactive protein and eGFR, each 20% greater estimated dietary phosphorus consumption was associated with 1.06 g greater LVM ($p < 0.001$). The strength of the study was the good control for confounding factors. The limitation of the study was the cross-sectional design.

Intima-media thickness

Itkonen et al. (2013) conducted a cross-sectional study to investigate the relationship between dietary phosphorus intake, in particular food additive phosphate, and intima-media thickness (IMT). A randomly sample of 1,920 subjects living in Helsinki, aged 37–47 years (females, n = 370; males, n = 176) was derived from the Population Register Centre in Finland. Out of the 1,920 initially enrolled subjects, 678 participated in the study. Subjects with renal dysfunction, post-menopausal females and with subjects with missing data were excluded from the analysis. Data on smoking status, information on dietary habits (3-day food records and FFQ) focusing on phosphorus, calcium and vitamin D, was obtained for all participants. Fasting blood samples and spot urine samples, weight and height, BP, and information on smoking habits and physical activity were also collected at the time of the visit. Common carotid artery IMT was measured using high-resolution ultrasonography. Mean phosphorus intake from diet (natural occurring phosphate) was 1 617 mg/day (SD = 428). Exposure estimate for phosphates as food additives (FAP) were derived from maximum EU regulation FAP content from the following foodstuffs: marinated meat, sausages, cold meat cuts, cola beverages and processed cheeses. A FAP score (1–6) was created by dividing subjects into tertiles of intake for each FAP group (meat products, cola beverages, processed cheeses), with score 0 indicating the lowest intake tertile, score 1 the middle tertile and score 2 the highest tertile. Then, the scores from different FAP sources were summed and each subject had a score of one to six. No significant association was observed between TP intake or FAP score and IMT after adjusting for sex, age, low-density/high-density lipoprotein cholesterol ratio, smoking status and IMT sonographer class. The strength of the study was the attempt to separate total phosphorus and FAP intake. The main limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality. Moreover, the FAP score is not very easily interpreted.

Coronary artery calcification

Kwak et al. (2014) conducted a cross-sectional study (n = 23,652) to study the relationship between phosphorus intake and phosphorus serum levels and coronary artery calcification (CAC). Eligible participants had no CKD (estimated glomerular filtration rate ≥ 60 mL/min*1.73 m^2) and/or CVD. Participants (40.8 ± 7.3 years) were mainly (males 83%), who underwent, as part of health check-ups, cardiac computed tomographic estimation of CAC (scores, 1–100 and > 100). Dietary habits, including alcohol intake was assessed by a FFQ. Clinical data and information on physical activity and smoking were collected for all participants. In the multivariate analysis, adjusted for adjusted for age, sex, smoking status, alcohol intake, physical activity, body mass index, educational level, family history of CVD, medication for dyslipidaemia, diabetes mellitus, hypertension, glomerular filtration rate, albumin, ferritin, total calorie intake, calcium intake, phosphorus intake and calcium supplements, high serum phosphorus (≥ 3.9 mg/dL) was associated with high CAC scores, (OR: 3.33, 95% CI: 2.55–4.35, p-trend < 0.001). No association was found for high intake of phosphorus (≥ 965 mg/daily. The strength of the study is the large sample size and the good control of confounding factors. The limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality.

Summary of the results of the studies on dietary phosphorus/phosphates and cardiovascular-related outcomes

Two cohort studies (Alonso et al., 2010; Chang et al., 2014) and four cross-sectional studies; (Itkonen et al., 2013; Yamamoto et al., 2013; Kwak et al., 2014; Mazidi et al., 2017) investigated the relationship between dietary phosphorus and cardiovascular-related outcomes. Alonso et al. (2010) pooled the data of two cohort studies (7.1-year and 3.2-year cohort studies, n = 8,208) and found no association between phosphorus intake and hypertension. Chang et al. (2014) conducted a 3.4-year cohort study (n = 7,705) and found no association between high phosphorus intake (> 1,400 mg/day) estimated from a single 24-h recall, and cardiovascular specific mortality. The study of Yamamoto et al. (2013) studied the association between dietary phosphorus with LVM in 4,494 subjects and showed that each 20% greater estimated dietary phosphorus consumption was associated with 1.06 g greater LVM and it was statistically significant. Itkonen et al. (2013) studied the relationship between dietary phosphorus intake, in particular food additive phosphate, and IMT and found no association. Kwak et al. (2014) the relationship between phosphorus intake and coronary artery calcification and found no association. Mazidi et al. (2017) investigated the association between phosphorus intake and BP and found a statistically significant inverse correlation between phosphorus intake and BP. In conclusion, there is insufficient data in the cohort studies to link dietary phosphates intake to cardiovascular risk. Inconsistent results have been reported from cross-sectional studies.

One of the limitations of the epidemiological studies that assessed dietary phosphorus and CVDs outcomes was the use of food composition databases which might not include data on all phosphates used as food additives leading to underestimation of the total phosphate intake. Another limitation was the use the 24-h recall assessing food intake. It is known that a single day is unlikely to be representative of usual individual intake, especially for phosphorus. The number of days necessary for assessing micronutrients and energy intake seems to be at least 5 days. Thus, this misclassification error may have led risk estimates towards null.

Overall, there is insufficient evidence to link dietary phosphates intake to cardiovascular outcome.

3.6.2. Studies on serum phosphorus/phosphate and cardiovascular diseases-related outcomes[18]

Cardiovascular disease incidence and cardiovascular mortality

Chang et al. (2014) investigated associations between serum phosphorous and all-cause and cardiovascular mortality prospectively in 12,984 participants of NHANES III (mean age 44 years, 52% women, after excluding 181 participants with more than 24 h fasting times or inconsistent venepuncture times). Serum phosphorous was measured at baseline using the reaction of inorganic phosphorous with ammonium molybdate, measured by spectrophotometry. Age, sex, race, ethnicity, cigarette smoking (never, former or current), physical activity, and family income were self-reported, height, weight at baseline were measured using standardised methods. Participants were stratified by fasting-duration

[18] Due regard has been given to the convention in epidemiological studies for expression of the results as (serum/urine) phosphorus rather than phosphate. In this section we regard serum phosphorus to mean phosphate.

before venepuncture (≥ 12 h, 6,633 participants; < 12 h, 6,351 participants). Mortality data were obtained from the NHANES III Mortality File, and cardiovascular mortality was defined as International Classification of Diseases (ICD)-10 I00–178, and after a median follow-up of 14.3 years, 2,993 deaths had occurred. After adjusting the multivariable model for examination session (morning vs afternoon/evening), age, sex, African American race, Mexican ethnicity, poverty, inactivity, body mass index, smoking status, systolic BP, diabetes, non-HDL cholesterol level, ACR, eGFR and vitamin D status, high serum phosphorous was significantly associated with all-cause [HR Q1 vs Q4: HR: 1.74 (95% CI: 1.38; 2.20)] and cardiovascular (HR: 2.00; 95% CI: 1.36; 2.96) mortality in those with 12 h or more fasting before venepuncture, but not those with shorter fasting duration (HR: 1.08; 95% CI: 0.98, 1.32 and HR: 1.21; 95% CI: 0.88,1.67], respectively). A continuous analysis using linear splines shows a significant increase in all cause mortality (HR: 1.35; 95% CI: 1.05, 1.74) per mg/dL) and cardiovascular mortality (HR: 1.45; 95% CI: 1.05, 2.00 per mg/dL). The strength of the study was the large sample size and the long follow-up. The main limitation of the study was the lack of adjustment for diet.

Larsson et al. (2010) investigated associations between serum phosphorous and all-cause and cardiovascular mortality in 2,176 men of the Uppsala Longitudinal Study of Adult Men [mean age 50 years, after excluding participants lacking data on creatinine, Ca or Pi measurements (n = 139), or with $eGFR_{CG}$ of 60 mL/min* 1.73 m^2 or below (n = 7)]. Serum phosphorous (fasting blood samples, fasting from midnight) was measured at baseline using the reaction of inorganic phosphorous with ammonium molybdate, measured by spectrophotometry. Data on lifestyle, e.g. smoking habits and medical history, were obtained by questionnaire at baseline. Cardiovascular death (ICD-8 and ICD-9, codes 390–459; ICD-10 codes I00–I99) was established using the Swedish national cause-of-death register, and after a median follow-up of 29.8 years, 1,009 participants had died, of which 466 were due to CVDs. After adjusting for age, body mass index, smoking, high serum phosphorous (T3, >2.8 mg/dL vs T1, <2.5 mg/dL) was associated with cardiovascular mortality (HR 1.31; 95% CI: 1.06, 1.63) but not all-cause mortality (HR: 1.16; 95% CI: 1.00, 1.35). In a continuous model, all cause (HR 1.06; 95% CI: 1.01, 1.12 and cardiovascular mortality (HR 1.10; 95% CI: 1.02, 1.18) per SD increase) were both associated with serum phosphorus. This did not change materially by including only participants with $eGFR_{CG}$ > 90 mL/min* 1.73 m^2 (n = 1,777). Strengths of the study was the long follow-up time and the main limitation was the lack of adjustment for diet and physical activity.

Onufrak et al. (2009) investigated associations between serum phosphorous, all-cause mortality and coronary artery disease (CAD) incidence in 13,998 participants (7,923 women, mean age 54 years, after excluding those with missing serum phosphorous data (n = 150), self-reported history of stroke or CAD (n = 1,010), and those with eGFR below 60 mL/min* 1.73 m^2 (n = 392) or above 150 mL/min* 1.73 m^2 (n = 182) of the ARIC who were free from CAD at baseline. Serum phosphorous was measured in fasting blood samples using the DART method at baseline. Deaths were ascertained using a variety of methods, including official records, obituaries, hospital records and interviews with next of kin, and after a median of 13.2 years of follow-up, 1,546 participants had died. After adjusting for age, sex, black race, body mass index, diabetes, hypertension, total cholesterol, HDL cholesterol, triglycerides, current smoking, eGFR (by CKD-EPI formula), serum fibrinogen, post-menopausal status and hormone replace therapy (HRT), high serum phosphorous (> 3.8 mg/dL vs < 3.1 mg/dL) was associated with an increased risk of CVDs (HR: 1.45; 95% CI: 1.04, 2.01) and all-cause mortality (HR. 1.45; 95% CI: 1.12, 1.88) was found for men but not for women. Strengths of the study were the long-term follow-up time and the sample size; the limitations were the self-report assessment of the outcomes in some cases and the lack of adjustment for diet and physical activity.

Dhingra et al. (2007) conducted a cohort study on 3,368 subjects within the Framingham Offspring study (mean age, 44 years; 51% of women) to investigate the association between serum levels of phosphorus and calcium and CVD incidence. All subjects with CKD and/or CVD were not included in the study. Information on smoking habits and alcohol consumption was obtained from all participants. Weight, height, BP, total cholesterol, HDL cholesterol, serum albumin, blood glucose, haemoglobin, C-reactive protein and triglycerides were all measured at baseline and every 4 years. Subjects with eGFR of less than 60 mL/min* 1.73 m^2 were excluded from the study. After a follow-up of 16.1 years, 524 incident CVD cases (159 events in women) were identified through reviewing hospital records, physician office visit notes, and pathology reports. CVD was defined as fatal or nonfatal myocardial infarction, angina pectoris (stable or unstable), cerebrovascular events (stroke or transient ischaemic attacks), peripheral vascular disease, or congestive HF. After adjusting in the multivariate model for age, sex, BMI, diabetes, BP, hypertensive drug use, smoking, alcohol consumption, total high-density cholesterol ratio, haemoglobin, serum albumin, eGFR, proteinuria and protein C-reactive protein, high levels of serum phosphorus was associated with an increased CVD risk in a dose response manner

(Q4 = 3.5–6.2 mg/dL; HR: 1.55, 95% CI: 1.16–2.07, p trend = 0.04). The increased risk remained statistically significant in the model in which up-dated CVD risk factors every 4 years were included and in the model that excluded subjects with proteinuria and with an eGFR of 90 mL/min* 1.73 m^2 or lower. The strength of the study was the long follow-up time. The limitation of this study was the lack of control for diet and physical activity.

Foley et al. (2008) conducted a US multicentre cohort study (Atherosclerosis Risk in Communities) to investigate the relationship between calcium phosphate levels and coronary heart disease, stroke and death. Out of 15,732 subjects (mean age 54.2 years, SD = 5.7) initially enrolled, a total of 13,816 subjects were included in the analysis. Demographic and clinical data was collected at baseline for all participants. Information on smoking habits, alcohol consumption and dietary habits was obtained for all participants. FFQ (61-item instrument) was used to assess dietary habits. Population phosphorus and calcium intake was 14.2 mg/kg (SD = 6.2) and 8.7 mg/kg (SD = 5.3), respectively. Serum phosphate and calcium was also measured at baseline. Mean serum levels of phosphate and calcium was 3.4 (SD = 0.5) mg/dL and 9.8 (SD = 0.4) mg/dL, respectively. The mean level of eGFR was 93.1 (SD = 21.5) per mL/min* 1.73 m^2. After 12.6 years of follow-up, 141 cases of coronary heart diseases and 44 cases of stroke were identified. In this study, dietary intake of phosphorus was associated with serum phosphate ($p < 0.0001$). In the multivariate analysis, adjusting for age, demographic characteristics, comorbid conditions, serum albumin and eGFR, serum phosphorous (per 0.5 mg/dL) was associated with both stroke (HR: 1.11, 95% CI: 1.02–1.21) and death (HR: 1.14, 95% CI: 1.09–1.20). No association was found for serum phosphate and coronary heart disease (HR: 1.03, 95% CI: 0.98–1.08). For calcium-phosphate product (per 5.5 mg^2/dL^2) risk estimates for coronary heart diseases, stroke and death were as following: HR: 1.03, 95% CI: 0.98–1.08; HR: 1.15, 95% CI: 1.05–1.26; and HR: 1.15, 95% CI: 1.09–1.20. The strength of the study was the large sample size and the good follow-up time. The limitation of the study was the lack of data on the number of people lost in the follow-up, many missing values in the exposure variables; people with CVDs were not excluded from the study; lack of adjustments for dietary variables, BMI, BP and physical activity.

Onufrak et al. (2009) investigated associations between serum phosphorous all-cause mortality and CAD incidence in 13,998 participants [7,923 women, mean age 54 years, after excluding those with missing serum phosphorous data (n = 150), self-reported history of stroke or CAD (n = 1,010), and those with eGFR below 60 mL/min* 1.73 m^2 (n = 392) or above 150 mL/min* 1.73 m^2 (n = 182)] of the ARIC who were free from CAD at baseline. Serum phosphorous was measured in fasting blood samples using the DART method at baseline. Incident CAD was defined as definite or probably myocardial infarction (fatal or non-fatal) or death due to CAD. CAD events were detected through annual interviews and surveys of hospital records, and after a median of 13.2 years of follow-up, 992 participants experienced incident CAD. After adjusting for age, sex, black race, body mass index, diabetes, hypertension, total cholesterol, HDL cholesterol, triglycerides, current smoking, eGFR (by CKD-EPI formula), serum fibrinogen, post-menopausal status and HRT, high serum phosphorous (> 3.8 mg/dL vs < 2.9 mg/dL) was associated with CAD incidence in men (HR: 1.45; 95% CI: 1.04; 2.01) but not in women (HR: 0.95; 95% 0.63; 1.41). Strengths of the study were the long-term follow-up time and the sample size. The limitations were the self-report assessment of the outcomes and the lack of adjustment for diet and physical activity.

Dhingra et al. (2010) investigated, within a cohort study (Framingham Offspring study), the association between serum phosphorus and incidence of HF (n = 3,666). It was also studied, using a cross-sectional design, the relationship between serum phosphorus and echocardiographic left ventricular mass, dimensions and systolic function. Subjects with previous myocardial infarction and/or atrial fibrillation (AF) and/or eGFR < 60 mL/min* 1.73 m^2 were excluded from the analysis. In total, 3,300 participants [1,616 men, mean age 44.7 years (SD = 10.3); 1,684 women, mean age 44.0 years (SD = 9.9 years)] were included in the analysis. Clinical data and information on smoking and alcohol were obtained for all participants. The mean eGFR (mL/min* 1.73 m^2) was 106 (SD = 43) for men and 114 (SD = 76) for women. After a mean of 17.4 years of follow-up, 157 cases of HF were identified. After pooling sex-specific quartiles and controlling for age, sex, BMI, diabetes mellitus, systolic BP, treatment for hypertension, smoking, total cholesterol/HDL cholesterol ratio, valve disease, albumin, haemoglobin, eGFR and proteinuria, subjects in the fourth quartile of serum phosphorus (mean: 3.8 mg/dL for women and 3.6 mg/dL for men) had twice the risk of having a HF in comparison to subjects in the first quartile (HR: 2.09; 95% CI: 1.28–3.40, p-trend = 0.02). In a subgroup analysis that included 1,850 individuals with eGFR > 90 mL/min* 1.73 m^2 and no proteinuria and with phosphorus lower than 4.5 mg/dL, the risk increased even more (HR: 3.11; 95% CI: 1.04–1.69, p-trend = 0.02). In the same model, using serum phosphorus as a continuous variable the risk remained (HR: 2.40; 95% CI: 1.29–4.46). After

adjusting for LVM, dimensions and left ventricular systolic function the risk associated with high phosphorus levels and incidence of HF remained in all models. The strength of the study was the long follow-up time. The limitation of the study was the lack of control for diet and physical activity.

McGovern et al. (2013) investigated the association between serum phosphate and cardiovascular events within the 'Quality Improvement in Chronic Kidney Disease' (QICKD) cluster randomised trial. Subjects with CKDs (n = 33,648, mean age 72.8 years, SD = 16.1 years) and subjects without CKDs (n = 24.184, mean age 52.8 years, SD = 17 years) were included in the study and were followed over a period of 2.5 years. Normal renal function was defined as an eGFR of 90 mL/min* 1.73 m^2 or more and absence of significant proteinuria. In the group with normal renal function, 133 strokes, 120 TIAs, 84 MIs, 110 coronary artery procedures, 45 other advanced CAD events, 77 new cases of HF and 521 deaths were identified during the 30 months of follow-up while in the group with CKD subjects, 291 strokes, 254 TIAs, 199 MIs, 222 coronary artery procedures, 77 other advanced coronary artery, 222 new cases of HF and 1,401 deaths were identified. After adjusting for sex, age, smoking, hypertension, diabetes and cholesterol, subjects with normal renal function and high serum phosphate (1.25–1.50 mmol/L) had an increased risk of cardiovascular events (OR: 1.36, 95% CI 1.06–1.74) in comparison to subjects with normal renal function and serum phosphate levels from 0.75 to 1.00 mmol/L. The risk was even higher for subjects with phosphate levels of 1.50 mmol/L or more, but it did not reach statistical significance (OR: 1.80, 95% CI: 0.89–3.63). In people with CKD, a statistically significant increased risk for cardiovascular events was found for phosphate levels above 1.25 mmol/L. Limitations of the study was the short time of follow-up the broad definition of cardiovascular events and the lack of control for dietary and physical activity.

Lutsey et al. (2014) within a US multicentre cohort study (ARIC) studied the relationship between serum magnesium, phosphorus and calcium and incidence of HF. Subjects who had a previous HF and/or missing information on the outcome and/or ethnic minorities were excluded from the analysis. A total of 14,709 (aged 45–64 years in the period from 1987 to 1989) were included in the analysis. Demographic information, medical history and medication use, dietary habits including alcohol consumption and lifestyle information such as smoking and physical activity were collected at baseline. After a median follow-up of 20.6 years, 2,250 incident HF events (ICD-9 codes from 428.0 to 428.9) were identified through calling by phone participants to ask information on hospitalisation, by reviewing local hospital discharges and by retrieving death certificates. Mean phosphorus levels were 3.43 (SD = 0.49 mg/dL). In the multivariate model, after adjusting for age, sex, race, centre, education, physical activity, smoking status, BMI, diabetes, systolic BP, hypertension medication use, lipid-lowering medication use, prevalent coronary heart disease (CHD), eGFR, low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglycerides and albumin, subjects with high serum phosphorus (median 4.1 mg/dL) had an increased risk for HF (median 4.1 mg/dL) (Q5 vs Q1, HR: 1.36; 95% CI: 1.18, 1.56, p-trend = 0.0005). After including magnesium and calcium in the models, the risk estimates did not change. The strength of the study was the large sample size. Limitations of the study were the inclusion of subjects also with eGFR below 60 mL/min* 1.73 m^2 and lack of control for dietary habits.

Hayward et al. (2017) conducted a retrospective cohort study within sentinel primary care networks of the Royal College of General Practitioners Research and Surveillance Centre to investigate if serum phosphate was a predictor of primary cardiac events. The study included 121,605 patients (18–90 years) free from CVDs. The serum phosphate level was the mean of up to five phosphate measurements before any cardiovascular event. The outcome was defined as any primary cardiac event of myocardial infarction, acute coronary syndrome or revascularisation procedures. After 5 and 9 years of follow-up (from the initial phosphate measurement), there were 1,595 and 2,268 events, respectively. Demographic data, smoking habits and biochemical and clinical data such as systolic BP, HDL cholesterol, LDL cholesterol, eGFR, diabetes status and blood markers HbA1c, corrected calcium, sodium, potassium and albumin data was obtained for all patients. In the 9-year review, subjects with phosphate levels of 0.75 mmol/L or less (OR: 1.89, 95% CI: 1.23–2.81) and subjects with phosphate levels above 1.25 mmol/L (OR: 1.83, 95% CI: 1.44–2.31), in comparison to subjects with phosphate levels between 1.0 and 1.25 mmol/L, had an increased risk of a cardiovascular event. The strength of the study was the large sample size and the limitation of the study was the use of administrative data, no clear indication of the confounding factors included in the models.

Lopez et al.(2013) investigated associations between serum phosphorous and AF in 14,998 participants [8,071 women, mean age 54 years, after excluding those who were of a racial group other than white or black (n = 103), those with prevalent AF at visit 1 (n = 37), low-quality or missing electrocardiograms (n = 242), missing phosphorus levels (n = 124), non-fasting blood samples (n = 485), missing covariates (n = 108) and eGFR < 15 mL/min* 1.73 m^2 (n = 18)] of the ARIC who

were free from AF at baseline. Serum phosphorous was measured in frozen fasting blood samples using a method based on ammonium molybdate at baseline. AF diagnoses were ascertained using electrocardiograms performed at study visits, hospital discharge codes and death certificates. During a median follow-up of 19.7 years, 1,656 incident AF occurred, and after adjusting for age, sex, race, study site, education, height, smoking, alcohol drinking, body mass index, diabetes, serum calcium (adjusted for albumin), systolic BP, diastolic BP, use of antihypertensive medications, eGFR (modelled as a spline), prevalent stroke, prevalent HF and prevalent coronary heart disease, high serum phosphorous (≥ 3.9 mg/dL vs ≤ 3.0 mg/dL) was not associated with increased risk of AF (HR: 1.15; 95% 0.98; 1.36). After stratification by eGFR, a significant association was only found in those participants with eGFR ≥ 90 mL/min* 1.73 m^2 (n = 10,149; 1,022 cases; (HR: 1.34; 95% CI: 1.09; 1.65), but not those with eGFR 60–90 mL/min* 1.73 m^2 (n = 4297; 587 cases; HR 0.91 [0.68; 1.21]) or eGFR < 60 mL/min* 1.73 m^2 (n = 243; 47 cases; HR 1.24; 95% CI: 0.44; 3.46). Strengths of this study are the sample size and duration; the limitations were the lack of adjustment for diet and physical activity.

Foley et al.(2009) investigated the association between serum phosphorous and coronary artery calcification in 3,015 out of 5,115 participants of the Coronary Artery Risk Development in Young Adults (CARDIA) study for whom data on serum phosphorous concentration at baseline and coronary artery calcium level after 15 years of follow-up were available (mean age at baseline 25.2 years, 54% women; 1,444 participants were lost at follow-up, 629 did not have data on coronary artery calcium and a further 27 did not have data on serum phosphorous). Serum phosphorous was measured in fasting (12 h) blood samples using a SMAC 12 continuous flow analyser, coronary artery calcification was assessed by different methods in different study centres, i.e. Imatron C-150 electron beam scanner, GE Lightspeed multidetector scanner or Siemens (Berlin, Germany) VZ multidetector scanner to calculate a calcification score. 9.6% of the study population had some artery calcification, but only 1.6% had moderate or severe calcification. After adjusting for age, sex, ethnicity, education, smoking status, prevalent diabetes, family history of MI, BMI, blood lipids and glucose, BP, eGFR, exercise, medication and diet (e.g. alcohol, calcium and phosphorous), serum phosphorous was significantly associated with calcification score category (0, 0–10, 10–100, 101–300 or 300 units, OR 1.17 (1.01; 1.34) per 0.5 mg/dL, and a calcification score above 10 (OR: 1.20; 95% CI: 1.01; 1.43). In categorical analyses, using quantiles, high serum phosphorous (> 3.9 mg/dL vs ≤ 3.3 mg/dL) was significantly associated with a calcification score above 10 (OR 1.60; 95% CI: 1.01; 2.55). These associations did not change materially after excluding participants with an eGFR below 60 mL/min* 1.73 m^2. The strength of the study was the long follow-up period and the limitations were the use of a logistic model and the use of a single 24-h dietary recall.

In summary, nine cohort studies on CVD incidence (Dhingra et al., 2007, 2010; Foley et al., 2008; Onufrak et al., 2009; Lopez et al., 2013; McGovern et al., 2013; Lutsey et al., 2014; Hayward et al., 2017) and two cohort studies on cardiovascular mortality (Larsson et al., 2010; Chang et al., 2014) were reviewed. Dhingra et al. (2007) conducted a cohort study on 3,368 subjects and observed that high serum phosphorus was associated with an increased CVD risk in a dose response manner. Foley et al. (2008) conducted a multicentre cohort study in 13,816 subjects and showed a positive association between serum phosphates and stroke incidence but not for serum phosphorus and coronary heart disease incidence. Onufrak et al. (2009) conducted a cohort study in 13,998 participants and showed that high serum phosphorous was associated with an increased risk for CAD incidence among men but not among women. Dhingra et al. (2010) in cohort study of 3,666 subjects showed that serum phosphorus was associated, in a dose-response manner, with an increased risk of HF. McGovern et al. (2013) in a cohort study of 24,184 subjects showed that high phosphorus levels were associated with an increased risk for cardiovascular events. Lutsey et al. (2014) within a US multicentre cohort study (n = 14,709) showed that high serum phosphorus was associated with an increased risk of HF. Hayward et al. (2017) conducted a retrospective cohort study on 121,605 subjects and showed an increased risk of cardiovascular events among subjects with both low (0.75 mmol/L or less) and high serum phosphorus levels (1.25 mmol/L or more). Lopez et al. (2013) in a cohort of 14,998 subjects showed that high serum phosphorous was not associated with the incidence of AF. Foley et al. (2009) investigated in a cohort study of 3,015 subjects the association between serum phosphorous and coronary artery calcification level and found a statistically significant association. Chang et al. (2014) in a cohort study of 12,984 subjects showed that high levels of phosphorus was associated with an increased risk of cardiovascular mortality. Larsson et al. (2010) in cohort study of 2,176 men showed an increased risk of cardiovascular mortality for those in the highest category of phosphorus.

Overall, there is evidence for a link between serum phosphorus and incidence of CVDs and some evidence to link serum phosphorus and cardiovascular mortality.

Coronary artery calcification

Kwak et al. (2014) conducted a cross-sectional study (n = 23,652) to study the relationship between phosphorus intake and phosphorus serum levels and CAC. Eligible participants had no CKD (eGFRrate ≥ 60 mL/min* 1.73 m^2) and/or CVD. Participants (40.8 ± 7.3 years) were mainly (males 83%), who underwent, as part of health check-ups, cardiac computed tomographic (CT) estimation of CAC (scores, 1–100 and > 100). Dietary habits, including alcohol intake was assessed by a FFQ. Clinical data and information on physical activity and smoking were collected for all participants. In the multivariate analysis, adjusted for adjusted for age, sex, smoking status, alcohol intake, physical activity, body mass index, educational level, family history of CVD, medication for dyslipidaemia, diabetes mellitus, hypertension, glomerular filtration rate, albumin, ferritin, total calorie intake, calcium intake, phosphorus intake and calcium supplements, high serum phosphorus (≥ 3.9 mg/dL) was associated with high CAC scores, (OR: 3.33, 95% CI: 2.55–4.35, p-trend < 0.001). No association was found for high intake of phosphorus (≥ 965 mg/daily). The strength of the study is the large sample size and the good control of confounding factors. The limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality.

Linefsky et al. (2011) in a cross-sectional study investigated the association between serum phosphorous and calcific aortic valve disease (n = 1,938) (70% women, mean age 73 years) participants of the cardiovascular health study (after excluding 1,428 participants with prevalent CVDs, 948 with insufficient amounts of serum and 378 with missing echocardiogram). Serum phosphorous was measured in fasting serum using time-rated colorimetric reaction with ammonium molybdate. Outcomes were aortic annulus calcitication (AAC) and aortic valve calcification (AVC), and mitral annular calcification (MAC). AVS was identified as aortic cusp thickening with normal aortic cusp, MAC was defined by an intense echocardiograph-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, short-axis or apical four-chamber view. The presence of AAC was similarly defined as increased echodensity of the aortic root at the insertions of the aortic cusps. Following adjustment for age, sex, race, eGFR, hypertension, diabetes, smoking, body mass index, LDL cholesterol, HDL cholesterol, statin use, serum calcium levels and clinic site, high serum phosphorous (> 4.0 mg/dL vs < 3.0 mg/dL) was significantly associated with aortic valve sclerosis (OR: 1.64; 95% CI: 1.10, 2.43) and mitral annular calcification (OR: 1.62; 95% CI: 1.10; 2.38), but not aortic annual calcification (OR: 1.32; 95% 0.90; 1.92). Analyses using serum phosphorous as a continuous variable showed a significant association only for aortic valve sclerosis (OR: 1.17; 95% CI: 1.04; 1.31) per 0.5 mg/dL increase). Strengths of this study is the number of confounders included. The limitation of this study is the cross-sectional nature as well as limited methodological information.

Park et al. (2016) investigated the association between serum phosphorous and coronary artery calcification in 2,509 (37% women, mean age 54 years old) patients undergoing coronary CT screening (after excluding those with eGFR below 60 mL/min* 1.73 m^2, albuminuria and previous history of overt vascular events. Serum phosphorous was measured using a clinical analyser, coronary artery calcification was quantified as the Agatston Score on coronary CT. Following adjustment for age, sex, diabetes, hypertension, body mass index, systolic BP, corrected serum calcium, albumin, haemoglobin A1c, LDL cholesterol and HDL cholesterol, high serum phosphorous (> 4 mg/dL vs < 3.2 mg/dL) was associated with a higher risk of an Agatston score above 100 [OR 2.11 (1.34; 3.32)]. The main limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality.

Criqui et al. (2010) investigated risk factors of artery calcification in 1,974 out of 6,814 participants of the MESA (mean age 58 years old). Patients without complete CT scan and free of CVD at base-line were excluded. Serum phosphorous was one risk factor and measured in 1,125 participants as part of an ancillary study, but no information about analytical methods or collection date were available, nor data on the composition of this subcohort, including calcification scores. Abdominal artery calcification was determined by electron-beam CT scan, whereas coronary artery calcification was measured by either electron-beam CT scan or multidetector CT, and the results used to calculate the Agatston score. At follow-up, 552 participants had developed abdominal artery calcification, 813 coronary artery calcification and 997 had both. After adjustment for age, sex, ethnicity, smoking status, blood-pressure, antihypertensive drug use, glycaemic status, HDL, LDL, lipid-lowering drug use and calcium, there were no statistically significant associations between serum phosphorous and abdominal artery

calcification (OR: 0.96; 95% CI: 0.79, 1.17] per SD [0.52 mg/mL] increase) or coronary artery calcification (OR: 1.11; 95% CI: 0.95; 1.31), although there was a statistically significant association between serum phosphorous and coronary Agatston score in a continuous model (ln(CAC + 1), $\beta = 0.21$; $p < 0.01$, per SD increase). The main limitation of this study was the lack of information on follow-up time and the lack of information on the subcohort for whom serum phosphorous data were available. Results were also not adjusted for diet or physical activity.

Linefsky et al. (2014) within the US Multi-Ethnic Study of Atherosclerosis (ARIC), a study was conducted (n = 6,814) to examine the association between phosphate metabolism biomarkers (serum phosphate, urine phosphate, PTH and FGF-23) and aortic valve calcification (AVC). Eligible criteria for participating in the study was aged 45–84 years and being free from clinical CVD. Out of the 6,814 subjects initially enrolled, 5,145 subjects were free of AVC aortic valve calcification. Demographic data, medical history, smoking status and medication history and fasting blood and urine samples were collected from all subjects. BP, eGFR, total and HDL were also measured at baseline. Mean serum phosphate levels was 3.67 (SD = 0.52 mg/dL) and median urine phosphate level was 44.1 mg/dL (IQR: 24.9–67.7 mg/dL). During the follow-up time (mean 2.4 years), 211 subjects developed AVC (4.1%). The mean eGFR was 99.81 (SD = 25.8) mL/min* 1.73 m^2 in subjects free from AVC (n = 5899) and 86.33 (SD = 24.5) mL/min* 1.73 m^2 in subjects with AVC at baseline. AVC prevalence was 13.2% and it was associated with higher phosphate levels (> 3.5 mg/dL). In the multivariate model, controlling for age, gender, ethnicity, study site, scanner type, BMI, BP, diabetes, smoking, LDL-cholesterol, HDL-cholesterol, 25-hydroxyvitamin D, eGFR, albumin to creatinine ratio and serum calcium, an increased risk, although not statistically significant, was found between high serum phosphate levels (> 4.0 mg/dL) and incident of AVC (HR: 1.25; 95% CI: 0.90–1.72) and high urine phosphate levels (67.9 mg/dL) and incident of AVC (HR: 1.18; 95% CI: 0.94–1.49). No association between PTH (HR: 1.10; 95% CI: 0.95–1.08) and serum FGF-23 pg/mL (HR: 1.10; 95% CI: 0.92–1.31, p-trend = 0.29) and incidence of aortic valve calcification was found. The strength of the study was the prospective design and relatively large sample size and the limitations were the short follow-up time, the inclusion of subjects not free of AVC at baseline and the lack of control in the models for diet and physical activity.

Arterial stiffness

Ix et al. (2009) within the MESA (Multi-Ethnic Study of Atherosclerosis) study investigated the association between serum phosphorus and ankle-brachial index in men and women (n = 1,370) In order to maximise the range of kidney function in the study sample., they selected all participants (n = 641) with an eGFR < 60 mL/min* 1.73 m^2 and randomly selected 1,000 participants from the remainder of the cohort with higher GFR. Serum phosphorous was measured in morning serum obtained after an overnight fast using reflectance spectrophotometry. Arterial stiffness was assessed using ankle brachial index (ABI, calculated as ratio of leg and arm systolic BP), pulse pressure and large and small artery elasticity (using pulse wave analysis). After adjusting for age, sex, race/ethnicity, diabetes, smoking (ever), BMI, LDL, HDL, log triglycerides, eGFR, log CRP and log albuminuria, high serum phosphorous (> 4.0 mg/dL vs < 3.0 mg/dL) was significantly associated with high ABI (ABI > 1.3; OR: 4.6, 95% CI: 1.6; 13.2), but no statistically significant associations were found for other measured of arterial stiffness. The limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality.

Carotid artery intima-media thickness

Onufrak et al. (2008) investigated the association between serum phosphorous and carotid IMT (cIMT) in 13,340 participants (57% women) of the community-based ARIC. Participants were without known coronary heart disease, stroke or renal disease. Participants with eGFR above 150 mL/min* 1.73 m^2 (n = 165) or below 45 mL/min* 1.73 m^2 (n = 47) were excluded from the analysis. Dietary data (FFQ) were available for 10,688 participants. Serum phosphorous was measured in fasting blood samples. cIMT was determined by measuring the far wall of the common carotid artery, the bulb and the internal carotid artery bilaterally. Following adjustment for age, sex, race, diabetes, hypertension, total cholesterol, HDL and smoking status and eGFR, cIMT was significantly associated with serum phosphorous in a dose-response manner (p-trend = 0.003). The limitation of the study was the cross-sectional design that impedes drawing conclusions of a possible causality.

Summary of the results of studies on serum phosphorus and other related outcomes

Kwak et al. (2014) conducted a cross-sectional study (n = 23,652) to study the relationship between phosphorus intake and phosphorus serum levels and CAC and found that high serum

phosphorus was associated with high CAC scores. Linefsky et al. (2011), in a cross-sectional study investigated the association between serum phosphorous and calcific aortic valve disease and found that high serum phosphorous was significantly associated with aortic valve sclerosis and mitral anular calcification but not aortic anular calcification. Park et al. (2016) in a cross-sectional study investigated the association between serum phosphorous and coronary artery calcification in 2,509 and found a higher risk of an Agatston score above 100 for those with high serum phosphorus levels. Criqui et al. (2010) in a cross-sectional study investigated risk factors of artery calcification in 1,974 and found no statistically significant associations between serum phosphorous and abdominal artery calcification or coronary artery calcification, although there was a statistically significant association between serum phosphorous and coronary Agatston score. Linefsky et al. (2014) in a cross-sectional study (n = 6,814) examined the association between phosphate biomarkers (serum phosphate, urine phosphate, PTH and serum FGF-23 and AVC and found no statistically significant association between high serum phosphate and urine phosphate levels and incident of AVC. Arterial stiffness was assessed using ABI, calculated as ratio of leg and arm systolic BP), pulse pressure and large and small artery elasticity (using pulse wave analysis and found that high serum phosphorous was significantly associated with high ABI-IX 2009 (Onufrak et al., 2008) investigated in a cross-sectional study the association between serum phosphorous and cIMT and found a statistically significant association, with a dose–response, between serum phosphorus and cIMT, with a dose-response.

Overall, because of the cross-sectional nature of all studies, the results finding an association between phosphorus serum levels and vascular calcification are uncertain and firm conclusion cannot be drawn.

3.6.3. Studies on urinary phosphorus/phosphate and cardiovascular-related outcomes[19]

Cardiovascular diseases and mortality

In 880 patients with stable CVD and normal kidney functions, serum phosphorus excretion were measured and the participants were followed for 7.4 years. Cardiovascular events and all-cause mortality were recorded (Palomino et al., 2013).

Urinary phosphorous excretion has been investigated as surrogate marker of phosphorous intake (Trautvetter et al., 2018), and it has been suggested that it can be used to estimate actual intake (Morimoto et al., 2014), but the data available are very limited. Human intervention studies (see below) suggest that urinary phosphorous excretion mainly reflects acute changes in intake and not long term, habitual intake.

The results of the study by Palomino are therefore not suitable to assess the risk of phosphorous intake.

3.6.4. Overall conclusion

- there is insufficient evidence to link dietary phosphates intake to cardiovascular outcome.
- there is some evidence to link serum phosphorus and CVDs incidence and some evidence to link serum phosphorus and cardiovascular mortality. However, serum phosphorus cannot serve as surrogate for phosphorus intake and studies did not control for important confounding factors.
- the link between phosphorus serum levels and vascular calcification seen in cross sectional studies does not allow drawing conclusions of a possible causality due the limitation of the study design.

3.7. Epidemiology studies on bone health

Few epidemiological studies investigated the role of phosphate on bone health in the general healthy population. Cross-sectional studies were not included in the evaluation.

Tucker et al. (2006) within the Framingham Osteoporosis study (1,413 women and 1,125 men) showed that cola-flavoured carbonated beverages containing phosphate were associated, in a dose response manner, with BMD in women but not in men. BMD was measured using dual-energy X-ray absorptiometry (DXA) at the right hip and the lumbar spine. After controlling for confounders such as

[19] Due regard has been given to the convention in epidemiological studies for expression of the results as (serum/urine) phosphorus rather than phosphate. In this section, we regard serum phosphorus to mean phosphate.

BMI, smoking, alcohol use, age, physical activity, calcium, vitamin D, caffeine intake from other sources other than cola and oestrogen use, negative linear associations were seen for cola consumption and BMD at each hip site femoral neck, ward's area trochanter, but not the spine, in women ($p < 0.001$). After stratifying the consumption of colas by caffeine content (caffeinated/decaffeinated), the effect remained only for ward's area but not for other hip. No association was seen between non cola-flavoured carbonated beverage consumption and BMD. In this study, total dietary phosphorus intake was not different from daily cola-flavoured carbonated beverage consumers and no cola-flavoured carbonated beverage consumers but the calcium-to-phosphorus ratio was lower.

Campos-Obando et al. (2017) combined data (n = 23,412) from two cohorts studies (Dutch Rotterdam study and the US Osteoporotic Fractures in Men study) to investigate the relation between serum phosphorus and incidence of fractures (self-reported in the US study and measured by X-ray in the Dutch Rotterdam study). In the pool analysis, serum phosphate was inversely associated with lumbar BMD measured by DXA in men ($\beta = -0.06$; 95% CI: −0.11 to −0.02) but not in women, after controlling for age, BMI, smoking and race. In the combined data analysis, after 6.6 years of follow-up a total of 1,825 fractures were recorded. In the multivariate analysis, adjusting for age, body mass index, smoking, serum levels of calcium, potassium, 25-hydroxyvitamin D, eGFR, phosphate intake, PTH, FGF-23 levels and phosphate levels (1 mg/dL increase), an elevated risk of fractures was observed for both women and men (HR: 1.47; 1.31–1.65) When the analysis was conducted using phosphate in quintiles (Q5 = 3.8 mg/dL), a dose–response was observed between serum phosphate and all types of fractures. Limitations of the studies were the outcome variable used in the US study (self-report) and the lack of control in both studies for physical activity and other potential confounders.

In summary, in the study of Tucker et al. (2006) the effect of phosphate on BMD was seen only in women, but not in man, consuming cola-flavoured carbonated beverages containing phosphate, while in the study of Campos-Obando et al. (2017) the effect of serum phosphorus on BMD was observed only in men and for lumbar spine BMD but not femoral neck BMD. In the study of Campos-Obano that investigated also the effect of serum phosphorus on the incidence of fractures, an increased risk of fractures was observed for both sex in a dose-response manner.

It is important to note that phosphate serum level is not considered to be appropriate to estimates phosphates intake. Therefore, more data on actual intake to assess the impact of phosphate intake on bone density and fractures are needed, in agreement with Vorland et al. (2017).

In conclusion, despite the effect of a high phosphorus intake on the activity of calcium-phosphate metabolism regulating hormones, there is insufficient evidence for an association between dietary phosphate intake and pathologically reduced BMD which is in accordance with evaluation from the NDA Panel (EFSA NDA Panel, 2005). There is also insufficient evidence for an association between serum phosphate and incidence of fractures.

3.8. Human studies

The Panel noted that in all human case reports and interventional studies the customary dietary phosphate intake was not reported and therefore the dose estimate only relates to supplementary phosphates intake observed in case reports or given in the clinical interventional studies.

3.8.1. Effects on kidney

Case series and case reports after acute administration

Publications were identified by a systematic literature search in which nineteen case of acutely severely impaired renal function are described after administration of phosphate as a treatment for bowel cleansing in preparation for colonoscopy (Fine and Patterson, 1997; Vukasin et al., 1997; Orias et al., 1999; Markowitz et al., 2004; Gonlusen et al., 2006; Santos et al., 2010; Cakar et al., 2012; Arikan et al., 2013).

For 15 of the patients, the dose was reported and the lowest dose which was causally related to an impairment of renal function was reported as 11,600 mg/day, in most cases consisting of two 5,800 mg doses taken 12–24 h apart (see Appendix P). In some of the cases, the patients recovered but, in several cases, renal impairment persisted and leading to CKD. One patient died. It is to be noted that many patients had an advanced age and pre-existing pathological conditions, e.g. hypertension. However, when baseline creatinine values have been measured, they resulted in the normal range (Aasebø et al., 2007).

The Panel noted that acute doses of phosphorus of 11,600 mg (165.7 mg/kg bw) given within 12–24 h can have deleterious effects on the kidney in some patients, in particular in the elderly (Study n. 2 in Appendix F; all but one patient were older than 55 years).

Histopathological evaluations of kidney specimens were published from patients with acute phosphate nephropathy after intake of phosphate salts as a treatment for bowel cleansing. The histological findings clearly showed calcium-phosphate crystals deposits within the cytoplasm of tubular epithelial cells and within tubular lumina (Aasebø et al., 2007; Vervaet et al., 2009; Markowitz and Perazella, 2009).

Interventional studies with short–term exposure

In seven clinical intervention studies with short-term exposure towards phosphorus, no impaired renal function was mentioned (see Appendix Q). The doses varied between 660 mg phosphorus and 2,500 mg phosphorus daily (11–40 mg P/kg bw/day) and the duration of the treatment was between 1 day and 14 days. The number of study participants encompassed 6–20 subjects.

Interventional studies with long-term exposure

Fifteen clinical studies were identified by a literature search in which subjects were exposed at least 1 month up to 2 years to phosphate (see Appendix R). The number of included subjects was small (between 5 and 13 subjects) with the exception of two studies in which 25 subjects (Ettinger, 1976) and 47 subjects (Miller et al., 1991) were treated. Doses between 350 and 7,200 mg/day phosphorus were given, mostly by the oral route with the exception of two studies where phosphorus was given by the intravenous route. The doses were an add-on to the phosphorus intake by the normal diet. In 14 of the 16 studies, the daily dose was at or below 2,000 mg phosphorus/day (28.6 mg/kg bw per day) and no influence on the renal function was described. The number of patients from all studies was 200.

In the clinical interventional trial of Dudley and Blackburn (1970), nine patients, age 35–71 years, were studied in a variety of conditions [hyperparathyroidism (4 patients); multiple myeloma (1 patient); renal calculi (4 patients)]. The patients received daily doses between 2,250 (32.1 mg/kg per day) and 4,500 mg daily (64.2 mg/kg per day) (one patient 2,250 mg/day, 7 patients 3,375 mg/day and 1 patient 4,500 mg/day) over a period of 9–87 months. In this study, creatinine clearance decreased in 2 patients (dose 4,500 mg/day for 78 months and 3,375 mg/day for 42 months). In all, but two patients (dose 2,250 mg daily for 16 months and 87 months, respectively) calcification in tissues were noted.

In the clinical interventional trial of Bernstein and Newton (1966), 10 patients, 16–69 years old, received phosphorus for studying its effect on kidney stone formation. 4 patients received 2,400 mg, 5 patients 4,800 mg and 1 patient 7,200 mg phosphorus daily for 4–24 weeks. At the end of the treatment period, in the dose group of 2,400 mg phosphorus daily, one patient had slightly reduced renal function; in the dose group of 4,800 mg phosphorus daily two patients had a reduced renal function and in the highest dose individual (7,200 mg phosphorus daily) creatinine clearance reduced to 50% of the pre-treatment value.

The Panel noted that in clinical trials daily doses up to 2,000 mg phosphorus (28.6 mg/kg bw per day) given over several months up to 2 years were tolerated without impairment of the renal function, whereas doses of 4,800 mg/day (68.6 mg/kg bw per day) and higher elicited renal impairment.

A meta-analysis of the studies with the aim to construct a dose–response relationship is hampered by the differing design, the differing duration, the low number of subjects per dose group and the insufficient reporting of study details. Nevertheless, these studies can give valuable information on the tolerability of phosphate doses in humans.

3.8.2. Effects on the gastrointestinal tract

In several of the clinical studies, it was noted that the subjects had soft stools or diarrhoea. In the study of Brixen et al. (1992) which was a short-term study of 7 days duration, 2 of 19 patients receiving 750 mg/day (10.7 mg/kg bw per day), 3 of 19 patients receiving 1,500 mg/day (21.4 mg/kg bw per day) and 7 of 20 patients receiving 2,250 mg/day (32.1 mg/kg bw per day) complained of gastrointestinal side effects. The Panel noted that the described effect is not to be seen as adverse but is classified as discomfort. However, when higher doses are given, such as the doses for bowel cleansing in preparation for colonoscopy (11,600 mg/day or 165.7 mg/kg bw) these doses acted as a cathartic agent and this effect has to be clearly seen as adverse.

3.8.3. Effects on PTH

Studies showing that phosphates intake induce PTH elevation are available (Reiss et al., 1970; Bell et al., 1977; Silverberg et al., 1986; Calvo and Heat, 1988; Calvo, et al. 1988; Calvo et al., 1990; Brixen et al., 1992; Kärkkäinen and Lamberg-Allardt, 1996). The studies were of short duration, mainly in young adults, and long-term studies measuring fractures incidence or bone density changes are lacking.

3.8.4. Effects on blood pressure

In an experimental interventional study in healthy subjects, Mohammad et al. (2018) investigated the influence of 6 weeks phosphorus intake in a dose of 17.15 mg/kg bw per day on top of the normal diet compared to a control group without additional phosphorus intake on a plethora of endpoints. Further treatment of 5 weeks was administered after a single intramuscular injection of vitamin D3 (600,000 U). An increase in P in serum was observed from 1.1 mmol/L to 1.3 mmol/L (week 6) and 1.4 mmol/L (week 11) in the group loaded with phosphorus with a corresponding elevation of urinary excretion of P. From further endpoints studied, FGF-23, Klotho and PTH were increased at week 6 as was urinary Klotho the values returning to normal within the next 5 weeks under treatment. Related to the administration of vitamin D3 serum 25(OH)D and serum 1,25(OH)D were elevated in both groups.

Mean 24-h systolic and diastolic BP as well as heart rate were increased in the phosphorus exposed group. The mean increase was 4 mm Hg (systolic) and 3 mm Hg (diastolic) and the pulse rate increased from 68 to 72 beats/min. Metanephrine and normetanephrine excretion in the urine was increased but within the reference range.

Further 41 parameters were measured and only the sodium excretion in both groups in urine was elevated due to the administration of phosphorus as sodium salt and of sodium in the control group. It is to be noted that none of the three parameters of endothelial function and arterial elasticity were changed by the phosphorus treatment.

The authors claim that the elevations of BP and pulse rate are caused by an elevated adrenergic activity. However, there is no physiological explanation and basis by which mechanism phosphorus intake may act on BP and pulse rate. Unfortunately, the authors did investigate only one single dose level of phosphorus which precludes drawing conclusions on the influence of higher and lower doses of phosphorus on the BP. A further shortcoming of the study is that the intake of phosphorus by the diet was not controlled by a dietary questionnaire and although some information can be drawn from the urinary concentration of phosphorus the amount of phosphorus excreted is not given in the publication. Although this publication is of interest, further confirmation of the findings is necessary and further dose levels have to be investigated.

3.9. Special populations – Infants below the age of 16 weeks

Sometimes in addition to natural phosphate content phosphates are added to infant formulas food for special medical purposes (FSMP) either for technological reasons and/or for its nutritional role (see Section 1.2). Special physiology and relevant toxicological and clinical studies are reviewed in the SNE publication (https://www.specialisednutritioneurope.eu/sne-literature-review-on-phosphates). A summary based on this document is given here.

Several clinical studies in infants consuming infant formula or FSMP with added phosphate have been performed. The outcomes investigated in these studies are generally effects on growth and/or on serum inorganic phosphate levels.

Most of these studies have investigated the effect of added phosphate (phosphoric acid, sodium phosphate, potassium phosphate or calcium phosphate) on growth parameters (including body weight, length and head circumference). These studies involved more than 2,600 infants and ranged in duration between 16 weeks and 1 year. In all studies, there were no statistical differences in the growth of the infant cohorts fed the various formulae from those of breast-fed infants and their growth matched the WHO growth standards.

There are a limited number of studies that assess the effect of formulas with or without added phosphate on serum inorganic phosphate concentration. Most of the studies have investigated the effects of formula not containing any added phosphate but where the phosphorus comes from natural presence in the milk ingredients. These studies indicate that infants fed formula have somewhat higher serum inorganic phosphate concentration than breastfed infants. However, the average serum inorganic phosphate concentration in formula-fed infants is within the normal reference range for serum inorganic phosphate laboratory values for infants.

Few studies have been performed where the effect on serum inorganic phosphate concentrations of infant formula with added phosphate has been investigated. Despite high phosphorus concentration in the supplemented formula the infants receiving this formula did not have higher serum inorganic phosphate concentrations

In conclusion, clinical studies in infants who consume either standard infant formula or FSMP with added phosphates demonstrate that the important clinical outcome, growth, is similar to WHO growth standard. This observation demonstrates that the addition of phosphates within the regulatory limits is of no concern. Furthermore, any adverse effect contributed to added phosphates would be through increased serum inorganic phosphate concentration. As demonstrated in a clinical study with high phosphorus, content in infant formula did not result in any significant increase of serum inorganic phosphate, which still fell within the normal range.

3.10. Mode of action, derivation of a phosphate-specific adjustment factor and derivation of ADI

3.10.1. Mode of action

Since nephrocalcinosis and/or tubular-interstitial nephropathy were identified as common endpoints in human and animal studies whereas bone and cardiovascular endpoints could not be confirmed as relevant for healthy human population in epidemiology studies, the only mode of action of interest concerns the effects on kidney.

Key events: In the process of renal excretion, phosphate is freely ultrafiltrated through glomerular barrier and reabsorbed in the proximal tubule by sodium-dependent transporters. When phosphate ultrafiltrate load exceeds the reabsorption capacity of the proximal tubule, the delivery of phosphate to the distal renal tubule increases disproportionately. As a consequence, calcium-phosphate concentration increases within the distal tubular lumen, up to formation of Ca-P crystals. It is important to note that this can occur in the distal tubule and in the collecting ducts, and that calcium-phosphate solubility is also a function of luminal fluid pH. In normal conditions, the pH values changes from 7.4 in the Bowman capsule to 6.6 in the distal tubule, a difference which does not strongly influence the solubility of calcium phosphate (see Section 3.1.1). Concerning the tubular fluid volume, another factor influencing phosphate solubility, it reduces along the tubular transit. When we compare the processes in man and rat, it can be assumed that the production of the urine is guided by the same principles. However, quantitative differences are evident. The estimated median volume of primary urine is 4.4 L /kg bw per day in the rat (Pestel et al., 2007) and 2.16 L/kg bw per day in man (range 1.60–2.8 L/kg bw per day; 5th to 95th percentile) (Poggio et al., 2009). The volume of urine excreted from the bladder is 67.8 ± 16 mL/kg bw per day in rats (Shevock et al., 1993) and 33.5 mL/kg bw per day in man (ICRP, 2002). According to these data, the rat produces twice the volume of the primary urine than a human and excretion of the urine volume from the bladder is similarly twice in rat compared to man. Hence, it can be assumed that along the lumen in the tubule and in the collecting duct of the kidney the volume in rat is twice of that in man. The volume of urine plays a deciding role as the concentration of calcium phosphate and its solubility depends on its volume. At the rat NOAEL for added phosphate with a daily dose of 76 mg/kg bw, the concentration in the primary urine and along the renal tubules is twice in humans compared to rat because the volume of the urine in humans is a factor 2 lower than the urine volume in rats.

Concordance of the key events in man and animal: In several short-term and subchronic rat studies, the endpoint calcification in the kidney has been observed in a dose-dependent manner with different phosphates (Chow et al., 1980; Mars et al., 1988; Ritskes-Hoitinga et al., 1989; Seo et al., 2011). The effect has also been observed in dogs (Schneider et al., 1981). The most reliable NOAEL from the short-term and subchronic studies was 500 mg/kg bw per day, corresponding to 116 mg/kg bw per day phosphorus in a 90-day study (Seo et al., 2011). In chronic rat studies, calcifications in the kidneys and tubular nephropathy was observed with NOAELs of 250 mg/kg bw per day with sodium triphosphate, corresponding to 63 mg/kg bw per day phosphorus and 250 mg/kg be per day sodium hexametaphosphate, corresponding to 76 mg/kg bw per day phosphorus (Hodge, 1959, 1960). The human interventional studies indicate that a dose of 2,000 mg/day (corresponding to 28.5 mg/kg bw per day) may be without an effect on the kidney function (references see Appendix Q). The mechanism and its key events are confirmed to be also relevant for humans by comparison of the histopathological changes described in the animal studies and in some publications describing the histopathology in human renal specimens. In these specimens, calcium phosphate crystals

precipitate predominantly in the distal tubule and collecting duct in patients with renal damage due to high intake of phosphate (Aasebø et al., 2007; Markowitz and Perazella, 2009; Vervaet et al., 2009). In addition, following high acute phosphate exposure renal tissue histology shows tubular atrophy and interstitial fibrosis that are signs of an irreversible chronic damage. It is likely that the persistence of crystal deposition within tubules prevents recovery of the acute damage leading to fibrosis (Markowitz et al., 2004). Vervaet et al. (2009) have investigated the fate of the crystal deposits in the renal tubule and observed overgrowth of the crystal deposits in the tubule, translocation into the interstitium and followed by inflammation and fibrosis. These histopathological changes are described in the Section 3.10.2 (derivation of ADI).

Temporal association: The key events, calcium-phosphate crystal formations in the distal tubules in the kidneys and impaired kidney function, are observed in humans with a temporal relationship to the intake of phosphate which depends on the dose. There are case reports indicating that acute renal failure was elicited with a single extremely high dose (160 mg/kg bw and more) whereas up to 2,500 mg/day (35.7 mg/kg bw per day) phosphorus (short-term exposure of up to 2 weeks) had no effect and calcifications were noted with a dose of 32.1 mg/kg bw per day in a long-term administration. As pointed out in Section 3.8, the dose of phosphorus is in addition to that found in the normal diet.

Strength, consistency and specificity of association of toxicological response with key events: There are no alternative mechanisms explaining the observed calcifications in the kidney and kidney impairment after phosphate exposure.

Biological plausibility and coherence: The observed effect is the consequence of the exposure of the kidney as it is the only excretory organ for phosphate with a salt that will deposit in the event of saturation. The effect is plausible and explained by physicochemical properties and the biology of the urine production in mammalia.

Uncertainties, inconsistencies and data gaps: The induction of precipitates in the kidney following exposure to calcium phosphate is well established. Clear dose responses have been reported in rats exposed to phosphates and in some human studies. In all the studies the dose of phosphorus is in addition to that found in the normal diet. Solid information on the phosphorus content of the feed could be retrieved for one of the rat studies (personal communication, Purina Korea, January 2019). Uncertainty and inconsistencies are very low concerning mode of action.

3.10.2. Derivation of a chemical-specific adjustment factor for phosphate

The evidence from epidemiological and human interventional studies is not suited to derive an ADI. In the epidemiological studies in which effects were seen concentrations of phosphorus in plasma/blood were related to the effects. However, plasma/blood phosphorus levels cannot be converted into dietary phosphorus exposure rendering the information on concentration–effect relationship unsuitable for the derivation of an ADI. The human interventional studies had major deficiencies as explained in Section 3.8.1. Therefore, evidence provided in the animal models has to be the basis for derivation of the ADI.

In this respect, it is important to note that the effects on kidney are consistent between humans and animals. The Panel considered which uncertainties factor would be appropriate and the Panel decided that the data are sufficient to derive and apply a chemical-specific adjustment factor for phosphate instead of the default factor of 100. Whereas the term uncertainty factor is used when the default value of 100 is used to convert the NOAEL into an ADI value, the term 'adjustment factor' is appropriate in cases where a substance specific factor (here: phosphate specific factor) is derived and used.

The default uncertainty factor of 100 is composed of a factor of 10 accounting for the interspecies differences between test species and humans and a second factor of 10 accounting for the interindividual differences in the human population. The two factors allow for interspecies differences and human variability in TK differences and toxicodynamics (TD). For the TK component of the interspecies factor, a value of 4 is then used when the extrapolation is made from the rat to the human (EFSA SC 2012 guidance on default value reference). This factor of 4 is based on allometric scaling from rat to humans. The remaining factor of 2.5 is attributed to the interspecies differences in TD. The uncertainty factor for interindividual differences has been further subdivided into two factors of 3.2 to allow to account for TK and TD differences. Whereas the factor of 10 describes the variability in the human population well as can be taken from an analysis of variability of doses of drugs, the subdivision into the two factors of 3.2 is not well supported by data.

In 2005, the IPCS/WHO proposed a framework indicating how chemical-specific TK and/or TD data can be used to replace the default factors or its subfactors. In line with the suggestions and following the extended approach as described in the IPCS/WHO document (2014), the quantitative analysis of the mode of action can aid to develop chemical-specific adjustment factors allowing for (interspecies and interindividual differences in TK and TD processes and their applications in chemical risk assessment has been recently reviewed (Bhat et al., 2017). The adverse effect of phosphate is due to the physico-chemical properties of calcium phosphate, the solubility, which is a substance property and is not species-specific. Hence, the TD part of the interspecies factor can be reduced to 1. With regard to the 'kinetic' part of the interspecies factor the renal handling of phosphate has to be considered. Phosphate is excreted by glomerular filtration and tubular reabsorption occurs, in both rats and humans. The solubility depends on the concentration of calcium phosphate which depends on the phosphate dose and the volume of the urine.

A chemical-specific adjustment factor for phosphate for interspecies differences in TK: the difference of the volume of the primary urine is the main determinant for the volume of urine in the tubule where calcium phosphate precipitation occurs and can be calculated for rat and humans. The estimated median primary volume is 4.4 L/kg bw per day $\pm$ 0.88 in the rat (Pestel et al., 2007) and 2.16 L/kg bw per day in man with a range of 1.60–2.8 L/kg bw per day (5th–95th percentile) in healthy kidney donors (Poggio et al., 2009). The ratio of the median glomerular filtration rate between rat and human (4.4 L/kg per day divided by 2.16 L/kg bw per day) equals 2. A ratio of 2 between rat and man results also from the volume of urine excreted from the bladder which is 67.8 $\pm$ 16 mL/kg bw per day in rats (Shevock et al., 1993) and 33.5 mL/kg bw per day in man (International Commission on Radiological Protection (ICRP), 2002).

From these data, we derived a phosphate-specific adjustment factor allowing for interspecies differences in TK of 2 giving phosphate-specific adjustment factors for interspecies differences of 2 (2 (TK) $\times$ 1(TD)) (see Figure 2).

A chemical-specific adjustment factor for phosphate for interindividual differences in TK: the same argument as for the TD interspecies subfactor is applicable for TD subfactor in humans which therefore is 1. For TK processes, creatinine clearance reflects the physiology of renal filtration of endogenous substances and xenobiotics and the normal range of healthy clinical values for adults and elderly are between 60 and 120 mL/min, with 90 mL/min often considered as the reference for creatinine clearance. Taking the ratio between the mean creatinine clearance (90 mL/min) and the lower end of the range (60 mL/min) gives a value of 1.5 (giving a ratio of 1.5 The Panel decided to increase this factor allowing for interindividual differences in TK to a value of 2 to provide a conservative estimate particularly to further take into consideration the healthy elderly population Hence, the phosphate specific adjustment factor for interindividual differences in TK was set a value of 2.

The composite phosphate specific adjustment factor accounting for interspecies and interindividual differences in TK and TD is then 2 $\times$ 2 = 4.

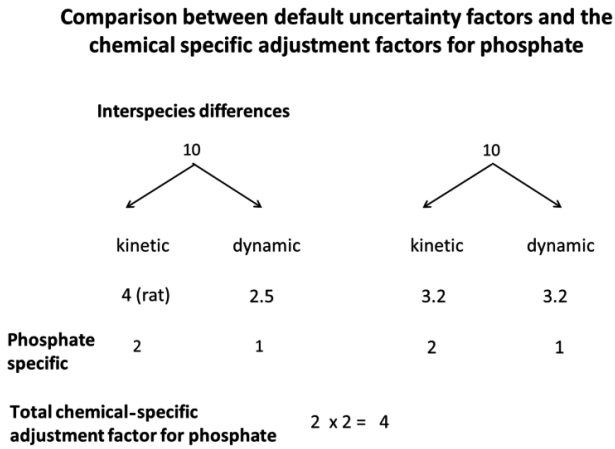

Figure 2: Comparison between default uncertainty factors and the chemical specific adjustment factors for phosphate

3.10.3. Minimum and maximum levels of phosphorus for infant formula (infants below the age of 16 weeks) and for infant formula for special medical purposes

For the age group of the infants below the age of 16 weeks, the special physiology of phosphate has to be considered. As pointed out in the introduction part of Section 3.5 the plasma levels of phosphate are twofold higher in the first 6 months of life compared with the adult plasma level indicating that the regulation of the plasma level is different in this age group compared to the adult man.

By regulation, the minimum and maximum total levels of phosphorus for infant formula are set at 25 mg/100 kcal and 90 mg/100 kcal, in the case of infant formula based on soy the maximum level is 100 mg/100 kcal. The minimum and maximum levels for infant formula for special medical purposes are set at 25 and 100 mg/100 kcal (Commission Delegated Regulation (EU) 2016/127 and Commission Delegated Regulation (EU) 2016/128, as well as Commission Directive 2006/141/EC and Commission Directive 1999/21/EC). These limits mean that at the high level consumption of 260 mL/kg bw per day by infant formula and by FSMP for infants (as calculated by EFSA, 2017) the exposure would be approximately between 44 and 175 mg/kg bw per day for phosphorus irrespective of whether phosphorus is delivered from the formula as nutrient or as food additive.

4. Discussion

Phosphates are normal constituents in the body and are regular components of the diet; however, no Tolerable Upper Intake Level (UL) (EFSA NDA Panel, 2005) has been established but in 2015 the NDA Panel set Adequate Intakes (AIs) values for various age groups.

In the context of this opinion, the Panel was in the special situation to derive an ADI for a substance which at the same time is a nutrient and a food additive. The ADI is the acceptable daily intake of a substance by exposure to phosphates from all sources including those naturally occurring in the diet, food additives and water.

4.1. Technical data

According to Commission Regulation (EU) No 231/2012, calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and dicalcium dihydrogen diphosphate (E 450(vii)) are described as 'insoluble in water' or 'sparingly soluble'. However, information from other sources indicates that tricalcium phosphate (E 341 (iii)) is soluble in water at 25°C (2.5 mg/100 g H_2O), and calcium dihydrogen phosphate (E 341(i)) is soluble in dilute hydrochloric acid (US National Library of Medicine, https://pubchem.ncbi.nim.nih.gov). Their solubilities in the gastrointestinal tract are not known especially given the presence of other dissolved ions and differences in pH that may be encountered. Thus, insoluble particles of these phosphate salts could theoretically be present within the gastrointestinal tract. It is conceivable that a small proportion of these particles may be in the nanorange. Based on the information received on the particle size of these phosphates, the Panel cannot exclude that particles in the nanorange can be present in phosphates when used as a food additive and, therefore, identified the need for additional information.

There are few validated official methods available for the determination of phosphates in foodstuffs permitted to contain phosphate additives in the EU. Those identified to date are summarised with standard methods listed by BVL (BVL, 2018) in Table 2. The scope of these methods covers ortho-, condensed and polyphosphate analytes, and most foodstuffs and beverages apart from those for infants (e.g. infant formula). The analytical techniques described in these methods are essentially limited to TLC and/or spectrophotometry, except for IC which is specified for the analysis of soft drinks. Data provided by CEFIC-PAPA provide evidence for the accuracy and precision requirements of standard methods for phosphate determination. For example, the total phosphorus is calculated as g/100 g reported to two significant figures (Documentation provided to EFSA n. 11). The Panel therefore identified the need for the development of analytical methods for phosphates in the range of foods permitted to contain them.

When considering the information submitted by the industry on the actual aluminium content in infant formula (final food), the Panel noted that the amount of aluminium may result in an exceedance of the respective TWI.

The Panel noted that the use of calcium phosphate (E 341), for which maximum limits for aluminium have been set in the EU specifications, can contribute to the total aluminium content in infant formula.

4.2. Kinetics

In humans, phosphorus deriving from food additives is mainly absorbed as free orthophosphate. The amount of orthophosphate absorbed from food additives is about 80–90%. No metabolism takes place and excretion is via the kidney through glomerular filtration and tubular handling. Data are available on the kinetics of disodium diphosphate, trisodium diphosphate, tetrasodium diphosphate and tetrapotassium diphosphate but not on dicalcium diphosphate and calcium dihydrogen diphosphate.

In animal models, the kinetics of phosphate are generally the same as in humans.

4.3. Animal toxicity data

There is a large number of toxicity studies on phosphates primarily in rats and mice but also in other species such as dogs, guinea pigs and hamsters

Data were not always available for all the authorised phosphates for all endpoints but the Panel considered possible to perform read-across between different phosphate additives.

Most studies are not performed according to the current guidelines and standard (OECD). The available data is however robust enough to be used to assess the safety of phosphates in animals and for NOAEL estimation.

For certain phosphate species added to feed, the number of water molecules were not specified. In these cases, the calculation of P content has been based on the anhydrous form.

It is clear from the available data that none of the phosphates are genotoxic *in vitro* or *in vivo* and that they are not carcinogenic. Furthermore, they do not present any risk for reproductive or developmental toxicity.

The only significant adverse effect observed with phosphates in standard toxicity studies is related to calcification of the kidneys and tubular nephropathy. These adverse effects are observed in acute, short-term, subchronic and chronic toxicity studies and in all species tested. The underlying mechanism behind these effects has been described in the mode of action (Section 3.9). As the renal effects are due to excess phosphate load and not to a direct effect of the cation and since all phosphate additives (E 338–341, E 343, E 450–542) are converted to orthophosphate, it is expected that all classes and structures of the phosphate additives would produce the same critical effects at high doses. Therefore, a single NOAEL can be established for all phosphates used as food additives. The NOAELs varied between the studies and phosphates tested but the reason for this variation is probably primarily due to doses of phosphates chosen and to spacing of the doses. Dietary factors, such as calcium and phosphate levels in the diet, may also contribute to the variability. Information regarding phosphate and calcium levels in the diets used are lacking in a most studies.

NOAELs and lowest-observed-adverse-effect-levels (LOAELs) could be identified from short-term, subchronic and chronic toxicity studies in rats. In subchronic studies, the highest reliable NOAEL relating to effects in the kidney was 500 mg/kg bw per day (corresponding to 116 mg P/kg bw per day), derived from a 90-day rat study with tetrasodium diphosphates performed according to OECD guidelines. The lowest phosphate level leading to effects on the kidney can be estimated to be approximately 1,000 mg/kg bw per day (corresponding to 233 mg P/kg bw per day) in the same study. In chronic toxicity studies, reliable NOAELs could be identified from two 2-year studies, 250 mg/kg bw per day (corresponding to 63 mg P/kg bw per day) and 250 mg/kg bw per day (corresponding to 76 mg P/kg bw per day) with sodium triphosphate (corresponding to pentasodium triphosphate) and sodium hexametaphosphate (corresponding to soluble sodium polyphosphate), respectively. The lowest level of phosphate causing an effect in the kidney was approximatively 750 mg/kg bw per day (corresponding to 229 mg P/kg bw per day) in a 2-year study with sodium metaphosphate.

In conclusion, the only significant adverse effect of phosphates in animals is nephrocalcinosis and tubule-interstitial nephropathy. The onset and progression of these effects appears quite rapid and the NOAELs and LOAELs for derived from subchronic and chronic studies are in the same range.

Although studies in animals report that high phosphorus intake causes bone reabsorption or decreased bone formation, the Panel considered that effects observed on bone metabolism and bone mineralisation in animals are not well characterised enough to derive an association with dietary high phosphate intake.

4.4. Epidemiology

The epidemiological studies reviewed here did not find consistent associations between dietary phosphorous intake and cardiovascular-related outcomes; all studies had important limitations such as the lack of control for important confounding factors (e.g. diet and physical activity). In addition, the use of food composition databases which might not include data on all phosphates used as food additives might lead to underestimation of the total phosphate intake. A further limitation is the considerable variability of phosphorus content in many foods depending on a number of factors such as food seasonality (Poulsen et al., 2015) and bioavailability of phosphorous from different sources (Karp et al., 2012). These factors make an accurate assessment of internal exposure from dietary sources unreliable.

Moreover, a single-day dietary record is unlikely to be representative of usual individual intake, especially for phosphorus. Multiple dietary records are necessary for assessing micronutrients. The misclassification of food intake can attenuate observed associations between intake and disease risk, and therefore risk estimates are biased towards the null.

Most studies reviewed using serum phosphorus concentration as a measure for exposure found an increase in risk for CVDs with high serum phosphorous concentrations (3.4–4.5 mg/dL). However, the concentrations observed were generally within the reference range (2.7–4.5 mg/dL). It is however important to be aware of the fact that serum phosphorus levels are influenced not only by diet but also by various metabolic factors. Although Moore et al. (2015) suggested that serum phosphorous concentrations are more sensitive to phosphate additives, the association between dietary intake and serum phosphorous is weak (R^2=0.03 in multivariable model including kidney function, BMI and albumin-to-creatinine ratio). In contrast, serum phosphorous concentrations change considerably throughout the day and follow a circadian rhythm (Ix et al., 2014), and these changes are affected by diet in a non-dose-response way. For example, phosphorous supplementation can affect the 24-h mean phosphorous concentration but it does not affect the serum concentration after an overnight fast (Portale et al., 1987). Moreover, serum phosphorous cannot be used to distinguish between different dietary phosphorous sources. Serum phosphorous concentration is therefore not a suitable surrogate marker of phosphorous intake, but rather a marker of other physiological processes. In summary, the results from epidemiological studies reviewed do not provide reliable information to assess the impact of phosphorous on CVDs.

Only two epidemiological studies investigated the role of phosphate on bone health in the general healthy population.

In the study of Tucker et al. (2006) the effect of phosphate on BMD was seen only in women, but not in man, consuming cola-flavoured carbonated beverages containing phosphate while in the study of Campos-Obando et al. (2017) the effect of serum phosphorus on BMD was observed only in men and for lumbar spine BMD but not femoral neck BMD. In the study of Campos-Obano that investigated also the effect of serum phosphorus and incidence of fractures, an increased risk of fractures was observed for both sexes, in a dose-response manner.

In summary, the results of these two studies do not provide sufficient and reliable data to assess the role of phosphate on bone health. More data on actual intake to assess the impact of phosphate intake on bone density and fractures are needed.

Studies showing that high phosphates intake induces PTH elevation are available (see Vorland et al., 2017). The studies were of short duration, mainly in young adults, and long-term studies measuring fractures incidence or bone density changes are lacking.

4.5. Case reports and clinical data in humans

Several case reports indicate that a high acute single dose of phosphate (160 mg/kg bw and more) can induce renal impairment.

Clinical interventional trials in which the doses were given on top of the normal diet were performed over several months. No impairment of the renal function was reported with daily doses up to 2,000 mg phosphorus (28.6 mg/kg per day) whereas doses of 4,800 mg/day (68.6 mg/kg per day) elicited renal impairment. Histopathological examinations of human kidney specimens from exposed patients showed similar findings as seen in animals. In several of the studies using phosphorus doses up to 2,000 mg/day, the subjects had soft stools or diarrhoea which is not to be seen as adverse but is classified as discomfort. However, when higher doses are given, such as the doses for bowel

cleansing in preparation for colonoscopy (e.g. 11,600 mg per person or 165.7 mg/kg bw) these doses acted as a cathartic agent and this effect has to be clearly seen as adverse.

In conclusion, in a chronic exposure setting the clinical data indicate that adverse effects on the kidney have been reported in human at added phosphates doses threefold lower than that causing adverse renal effects in animals.

4.6. Mode of action and discussion of uncertainty

The mode of action for the kidney impairment is precipitation of calcium phosphate which occurs in the kidney, the only organ for phosphate excretion, when the solubility is exceeded. Thus, the mechanism of action is related to a physicochemical property of calcium phosphate. From the identified mechanism of action which is species independent and independent from individual factors, the Panel derived a TD inter- and intraspecies factor of 1.

The maximum limit of solubility depends on the volume in which a certain amount of calcium phosphate is dissolved. Concerning the solubility of calcium phosphate in the primary urine, the urinary volume is relevant. The interspecies difference (rat vs man) in the volume of primary urine is 4.4 L/kg bw per day in rat vs 2.16 L/kg bw per day in man (see Section 3.10.2) resulting in a factor of 2. In other words, when a certain amount of phosphorus/kg bw per day would not exceed the solubility in rat with a urine volume of twice that in humans, the daily dose in humans not exceeding the solubility would be half of that amount.

For the variability of the urinary volume in humans, the Panel used information on the variability of the glomerular filtration rate in healthy subjects (between 60 and 120 mL/min). In order to account for the potentially lower glomerular filtration in subjects of the general population with a higher age and slightly impaired renal function, the Panel decided to consider the lower level of glomerular filtration rate resulting in an intraspecies factor for TK to 2. In other words, when a certain amount of phosphorus/kg bw per day which would not exceed the solubility in humans with a normal urine volume, the daily dose in humans with slight to moderate renal impairment not exceeding the solubility would be half of that amount.

Uncertainty:

(1) The first aspect is the application of the read across approach. Phosphates have been studied for all relevant endpoints required to assess the safety of a food additive. However, toxicological studies do not exist for all salts of phosphates authorised as food additives and the Panel applied a read across approach. Whereas no arguments point to the fact that the endpoints for toxicity of the various phosphates would differ it has to be assumed that the bioavailability and hence the dose for eliciting toxicity would differ with the solubility of the salts. In this respect as the calcium salts are only sparingly soluble or even insoluble in water, their bioavailability may be lower than that of other salts. Experimental data directly comparing the bioavailability of the various phosphate salts are lacking.

However, the lowest phosphate dose leading to effects in the kidney in short-term studies with monosodium phosphate dehydrate, the phosphorus dose is 123.8 mg/kg bw per day (Mars et al., 1988). The corresponding dose of the mixture of calcium dihydrogen phosphate and monosodium phosphate is 149.1 mg/kg bw per day. The comparison the two dose levels leading to effects on the kidney shows that the dose of the water-soluble and hence highly bioavailable monosodium phosphate dehydrate is only slightly lower (20%) than the dose of the sparingly soluble calcium dihydrogen phosphate and the water-soluble monosodium phosphate as a mixture. This indicates that phosphate is also available from calcium dihydrogen phosphate. The study from which the reference point is derived was a study with sodium metaphosphate which is water-soluble. Hence, the selected reference point overestimates the toxicity of the sparingly water-soluble and -insoluble calcium salts of phosphate, the extent might be around 20%.

(2) The second aspect is the selection of the key toxicity endpoint. Calcifications in the kidney have been identified as the most relevant endpoint for phosphorus which is observed in several species and also in man. Based on available data the selection of the key toxicity is unlikely to contribute to the uncertainty.

(3) The third aspect is the selection of the NOAEL. The highest reliable NOAEL from the short-term and subchronic studies was 500 mg/kg bw per day, corresponding to 116 mg/kg bw per day phosphorus in a 90-day study (Seo et al., 2011). In chronic rat studies

calcifications in the kidneys and tubular nephropathy was observed and the NOAELs of 250 mg/kg bw per day with sodium triphosphate (corresponding to pentasodium triphosphate) (63 mg/kg be per day phosphorus) and 250 mg/kg bw per day sodium hexametaphosphate (corresponding to soluble sodium polyphosphate) (76 mg/kg bw per day phosphorus) were identified (Hodge, 1959, 1960).

(4) The forth aspect is the derivation of the chemical specific adjustment factor for phosphorus. The derivation of the TD factor is based on the physicochemical property of the causing agent, calcium phosphate and this is applicable to the situation in rat and in humans as demonstrated by comparison of histopathology in both species. The TK interspecies factor of 2 is based on the species-specific different volumes of urine (see Section 3.10.2) and the TK intraspecies factor was set at 2 (see Section 3.10.2). For the interspecies TK factor of 2, the uncertainty could be estimated from the standard deviation of the measurements which would result in values between 1.44 and 2.85 indicating a relatively low uncertainty in the estimate of 2. The intraspecies TK factor was estimated from a study in healthy subjects and resulted in a factor of 1.5. The Panel decided to enlarge this factor to 2 to reduce the uncertainty in the extrapolation from the healthy subjects to the general population. The resulting total compound specific adjustment factor is then 4.

Considering all aspects which have to be discussed to characterise the uncertainty surrounding the ADI it can be stated that the uncertainty is low although a firm numerical number for the magnitude of the uncertainties cannot be given.

An ADI did not exist until now, and in 1982, JECFA concluded that the allocation of an ADI was not appropriate for phosphates 'as phosphorus is an essential nutrient and unavoidable constituent of food' (JECFA, 1982a). Therefore, JECFA assigned a 'maximum tolerable daily intake' (MTDI) of 70 mg/kg bw per day (expressed as phosphorus) for the sum of phosphates and polyphosphates, both naturally present in food and ingested as food additives. The rationale for the MTDI was that 'The lowest level of phosphate that produced nephrocalcinosis in rat (1% P in the diet) is used as the basis for the evaluation and, by extrapolation based on the daily food intake of 2,800 calories, gives a dose level of 6,600 mg P per day as the best estimate of the lowest level that might conceivably cause nephrocalcinosis in man'. In the evaluation, JECFA justified not to apply a safety factor with the argument that phosphorous was also a nutrient.

The solubility of calcium phosphate was identified as the relevant mechanism of action causing nephrocalcinosis in animals and man. In contrast to JECFA the Panel identified the urinary volume as relevant biological difference between rat and humans which influences the solubility of calcium phosphate. Taking also into account the variability of the urinary volume expressed as glomerular filtration rate in the human population the Panel derived a chemical specific adjustment factor of 4 for phosphorus.

4.7. Derivation of the ADI

In the context of this opinion, the Panel was in the special situation to derive an ADI for a substance which at the same time is a nutrient and a food additive. The ADI is the acceptable daily intake of a substance and includes exposure by food additives in addition to the exposure to the substance naturally occurring in the diet.

As explained in the discussion above the derivation of the ADI for phosphorus has to be based on the results of studies in animals. Three studies, one subchronic study and two chronic studies are available from which NOAELs could be derived. In the two chronic studies, the NOAELs were 63 mg/kg P bw per day and 76 mg/kg P bw per day (Hodge, 1959, 1960). However, the content of phosphorus in the background diet could not be identified. In the subchronic 90-day rat study performed according to OECD guidelines the NOAEL was 116 mg/kg bw per day phosphorus (Seo et al., 2011). The content of phosphorus in the diet could be retrieved (personal communication, Cargill Agri Purina Korea, 29 January 2019) and was calculated to result in a daily intake of 91 mg P/kg bw per day.

The Panel noted that the most appropriate reference point for derivation the ADI would be a NOAEL from a chronic study. Among the present two chronic studies, the higher NOAEL of 76 mg P/kg bw per day has been selected. Considering that ADI includes exposure by food additives in addition to the substance naturally occurring in the diet, the content of the phosphorus in the animal diet has to be taken into account. The Panel considered the content of phosphorus retrieved for Seo et al. study as an appropriate estimate of a standard animal diet which is also in conformity with phosphorus

content in laboratory animal diets from different sources (Ritskes-Hoitinga et al., 1991; Nutrient Requirements of Laboratory Animals, 1995).

Adding the dietary P of 91 mg/kg bw per day to the NOAEL of 76 mg P/kg bw per day gives a value of 167 mg P/kg bw per day. To this value, the chemical-specific adjustment factor for phosphate of 4 is to be applied resulting in an ADI value of 42 mg/kg bw per day, rounded to 40 mg/kg bw per day.

The Panel noted that this ADI would be the same if derived from the 90-day study. Since this is a subchronic study an adjustment factor of 2 should be applied (EFSA guidance 2012) resulting in a NOAEL of 58 mg P/kg bw per day. Adding the dietary P of 91 mg/kg bw per day to the adjusted NOAEL of 58 mg P/kg bw per day gives a value of 149 mg P/kg bw per day. Following the application of the phosphorus-specific adjustment factor of 4, this would result in an ADI of 37 mg/kg bw per day.

The Panel noted that the ADI of 40 mg P/bw per day does not apply to humans with moderate to severe reduction in renal function since the adjustment factor for intraspecies variability covers only individual with slight renal impairment.

The EFSA NDA Panel has not set an upper level for phosphorus but a 'safety' level of intake. The ADI of 40 mg/kg bw per day would result in an intake level of 2,800 mg P per person per day for a 70 kg adult person which is within the limits of the safety intake level of 3,000 mg P/person per day set by the EFSA NDA Panel (2005).

The newly derived ADI value for P compares well with consumption data from epidemiological studies. The mean dietary consumption was 1,373 mg phosphorus per day in adult subjects in the NHANES studies 2001 to 2014, the mean intake of phosphorus in adults from the diet alone was 1,725 mg/day with a P95 intake of 2,855 mg/day in a recent Norwegian survey (VKM Report 2017: 18) and the highest phosphorus dietary intake in the epidemiological studies reviewed (see Appendix S) was 3,600 mg/day. In contrast, the MTDI of JECFA (1982a) of 70 mg phosphorus/kg bw per day (equally to 4,900 mg phosphorus per adult person per day, assuming 70 kg body weight) is higher that the exposure reported in the cited epidemiological studies.

4.8. Exposure assessment

Phosphates (E 338–341, E 343, E 450–452) are authorised for 108 different uses (corresponding to 65 different food categories) according to Annex II to Regulation (EC) No 1333/2008 and data were received for most of the uses in which the food additives are authorised to be added.

To assess the dietary exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives, the exposure was calculated based on two different sets of concentration data: (1) MPLs as set down in the EU legislation (defined as the *regulatory maximum level exposure assessment scenario*); and (2) reported use levels (defined as the *refined exposure assessment scenario*).

While analytical data were used to consider the exposure to phosphorus from all dietary sources.

As mentioned above, in the context of this opinion, the Panel was in the special situation to assess the safety of food additives, phosphate salts, which are also nutrients. The Panel based its assessment on the toxicity of phosphorus (phosphate moiety). Since the ADI encompasses the phosphorus intake from natural sources and from food additives sources, the usual exposure assessment using the reported use levels of the food additives was not appropriate to characterise the risk linked to the exposure to phosphorus and the exposure assessment was based on analytical data of the total phosphorus content of foods. In other contexts, the evaluation of the adverse effects of nutrients serve as a basis to set ULs (EFSA NDA Panel, 2006). The Panel noted the lack of a harmonised procedure to assess the safety and set HBGVs for substances that are at the same time food additives and nutrients. The Panel considered that there is a need for developing a general approach to be followed in the case a food additive is also a nutrient.

Based on the reported use levels, the Panel calculated two refined exposure estimates based on different assumptions as described in Section 3.4.1: a *brand-loyal consumer scenario* and a *non-brand-loyal scenario*. The Panel considered that the refined exposure assessment approach resulted in more realistic long-term exposure estimates compared to the *regulatory maximum level exposure assessment scenario*.

The exposure estimates in the *regulatory maximum level exposure assessment scenario* were between 12 and 113 mg P/kg bw per day at the mean and between 21 and 196 mg P/kg bw per day at the 95th percentile for all population groups (Table 5b). The Panel noted that the estimated long-term exposures based on this scenario are very likely conservative, as this scenario assumes that all foods and beverages listed under the Annex II to Regulation No 1333/2008 contain phosphates (E 338–341, E 343, E 450–452) as food additives at the MPL.

Considering the *refined brand-loyal exposure assessment scenario,* estimated exposure to phosphates (E 338–341, E 343, E 450–452) was between 2 and 53 mg P/kg bw per day at the mean and between 9 and 69 mg P/kg bw per day at the 95th percentile for all population groups.

For the *refined non-brand-loyal exposure assessment scenario*, estimated exposure to phosphates (E 338–341, E 343, E 450–452) ranged between 1 and 48 mg P/kg bw per day at the mean and between 3 and 62 mg P/kg bw per day at the 95th percentile for all population groups (Table 5b).

The Panel considered that for the main food category (bread and rolls) contributing to the exposure estimates, brand-loyalty would not be expected and therefore selected the refined non-brand loyal scenario as the most relevant exposure scenario for the safety evaluation of phosphates (E 338–341, E 343, E 450–452) for toddlers, children, adolescents, adults and the elderly. Dietary exposure to phosphates (E 338–341, E 343, E 450–452) according to this exposure scenario was maximally 11 mg/kg bw per day at the mean level and 26 mg/kg bw per day at the high (P95) level. For infants, infant formulae were the main contributing food category, and the brand-loyal scenario should be considered.

For the food supplements consumers only, mean exposure to phosphates (E 338–341, E 343, E 450–452) from their uses as food additives ranged from 275 mg P/person per day for children to 1,541 mg P/person per day for the elderly. The 95th percentile of exposure to phosphates (E 338–341, E 343, E 450–452) ranged from 753 mg P/person per day for adolescents to 7,292 mg P/person per day for adults. The Panel noted the high levels for food supplements compared to therapeutic use (see Section 3.8.1). According to data providers, in a number of cases, the phosphates are added principally as nutrient substance and not as additives. However, in other cases, the addition of phosphates (e.g. higher reported use levels) is due to their technical requirements as food additives rather than an intended use as nutrient sources. The Panel noted the high intakes resulting from such levels and the potential risk for people who might consume food supplements regularly.

The Panel calculated that out of the foods authorised to contain phosphates (E 338–341, E 343, E 450–452) according to Annex II to Regulation (EC) No 1333/2008, a minimum of 30 (for children) to a maximum of 93% (for infants) of the amount of food consumed (by weight) per population group was reported to potentially contain phosphates (E 338–341, E 343, E 450–452) as food additives.

The exposure assessments were influenced by several uncertainties (Table 9). The Panel noted that most of Mintel subcategories were included in the current exposure assessment (missing food categories are alcoholic beverages, some vegetables, see Section 3.3.2). The percentage of foods per subcategory labelled to contain phosphates (E 338–341, E 343, E 450–452) was on average of 9.6% whereas in the assessment, it was assumed that 100% of the foods belonging to an authorised food category contained the additive. The Panel noted that an exposure assessment based on the premise that all of the foods contain phosphates would probably lead to an overestimation of the dietary exposure which represents the largest uncertainty.

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to phosphates (E 338–341, E 343, E 450–452) from their use as food additives according to Annex II in European countries considered in the EFSA European database for the *regulatory maximum level exposure scenario*. For the *refined estimated exposure scenario*, uncertainties would also lead to an overestimation of exposure to phosphates (E 338–341, E 343, E 450–452).

The Panel also noted that the refined exposure estimates are based on information provided on the reported level of use of phosphates (E 338–341, E 343, E 450–452). If actual practice changes, these refined estimates may no longer be representative and should be updated.

Scenarios based on uses and use levels estimating exposure including the proposed extension of use were performed. The proposed extension of use did not show any change in the total estimated exposure probably because the proposed change in the authorised use of the FC 05.2 does not add a large number of foods compared to the current authorisation.

Exposure to phosphates from the whole diet was estimated using mainly analytical data *(estimated exposure scenario based on analytical data)*. Not all available data could be included in the assessment but most of the foods consumed were taken into account in this estimate.

In this scenario, the exposure exceeds the ADI of 40 mg/kg bw per day in infants from 12 weeks to 11 months, toddlers and children both at the mean and high level. In adolescents, the high level is also exceeding the ADI of 40 mg/kg bw per day.

Both estimates using reported use levels and analytical data are limited by several uncertainties described in exposure section. Although caveats related to these estimates, exposure from food additives for all population groups except infants would indicatively contribute between 6 and 21% of the total mean intakes. For infants from 12 weeks to 11 months, the percentages would range between 12 and 30%.

To compare the *estimated exposure scenario based on analytical data*, with the exposure published in other opinions and surveys the mean exposure to phosphorus was calculated as the exposure per person per day and compared to exposure data from surveys. The values ranged from 254 mg P/person per day in infants to 1,625 mg P/person per day for adults, and the high exposure (95th percentile) from 331 mg P/person per day in infants to 2,728 mg P/person per day for adults.

Exposure estimates of phosphorus using the same methodology (consumption data from national dietary surveys and levels of phosphorus in food from analytical measurement) was also performed in the NDA Panel opinion (EFSA NDA Panel, 2015). Intake estimates from the 2015 opinion and the current estimates are very much similar per population groups. Foods in both opinion are not classified under the same categories but food categories contributing the most to the mean exposure are also the same: milk and dairy products, grains and grain-based products and meat and meat products in EFSA, 2015; unflavoured pasteurised and sterilised (including UHT) milk, bread and rolls and meat products for EFSA, 2018 (this opinion).

The high level of exposure to phosphorus coming from food supplements is reflected also in the dietary exposure in the food supplements consumers only scenario using analytical data.

Direct comparison of exposure based on analytical data with exposure reported in the epidemiological studies is not readily achieved due to differences in methodologies applied. Whereas comparison between such data is indicative only, the exposure levels are reasonably similar.

4.9. Infants and young children

By regulation, the minimum and maximum total levels of phosphorus for infant formula are set at 25 and 90 mg/100 kcal, in the case of infant formula based on soy the maximum level is 100 mg/100 kcal. The minimum and maximum levels for infant formula for special medical purposes are set at 25 and 100 mg/100 kcal (Commission Delegated Regulation (EU) 2016/127 and Commission Delegated Regulation (EU) 2016/128, as well as Commission Directive 2006/141/EC and Commission Directive 1999/21/EC). These limits mean that at the high level consumption of 260 mL/kg bw per day by infant formula and by FSMP for infants (as calculated by EFSA, 2017), the exposure would be approximately between 44 and 175 mg/kg bw per day for phosphorus irrespective of whether phosphorus is delivered from the formula as nutrient or as food additive. Given the limits set by existing regulation, it seems not appropriate to use the ADI set for food additives only for infants formulae, nor is necessary to derive a numerical ADI applicable for this age group.

5. Conclusions

Considering the overall database relevant for phosphoric acid–phosphates – di-, tri- and polyphosphates, the Panel derived a group ADI for phosphates expressed as phosphorus of 40 mg/kg bw per day from a chronic study. This ADI corresponds to an acceptable intake of phosphorus of 2,800 mg/day for an adult of 70 kg. This is within the level of 3,000 mg/day indicated by the EFSA NDA Panel (2005) as being tolerated by healthy individuals.

The Panel considers that the group ADI of 40 mg/kg bw per day, expressed as phosphorus, is protective for healthy adults because it is below the doses at which clinically relevant adverse effects were reported in short-term and long-term studies in humans. However, this ADI does not apply to humans with moderate to severe reduction in renal function. Ten per cent of general population might have CKD with reduced renal function and they may not tolerate the amount of P per day which is at the level of ADI. The total phosphorus content of foods (naturally occurring and added as additives) is not mandatory to be reported on food labels.

The Panel noted that the exposure estimates based on analytical data exceeded the proposed ADI for infants, toddlers and children at the mean level and for infants, toddlers, children and adolescents at the 95th percentile. The Panel also noted that P exposure from food supplements exceeds the proposed ADI.

The Panel concluded that the available data did not give rise to safety concerns in infants below 16 weeks of age consuming formula and food for medical purposes. When receiving data on the content of contaminants in formula, the Panel noted that the high aluminium content may exceed the TWI.

6. Recommendations

The Panel recommends that:

- The EC considers setting numerical Maximum Permitted Level for phosphates as food additives in food supplements.
- The European Commission considers revising the current limits for toxic elements (Pb, Cd, As and Hg) in the EU specifications for phosphates (E 338–341, E 343, E 450–452) in order to ensure that phosphates (E 338–341, E 343, E 450–452) as a food additive will not be a significant source of exposure to those toxic elements in food.
- The European Commission considers revising the current limit for aluminium in the EU specifications for the use of calcium phosphate (E 341).
- The European Commission to consider revising the current EU specifications for calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) to include characterisation of particle size distribution using appropriate statistical descriptors (e.g. range, median, quartiles) as well as the percentage (in number and by mass) of particles in the nanoscale (with at least one dimension < 100 nm) present in calcium dihydrogen phosphate (E 341(i)), calcium hydrogen phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), dimagnesium phosphate (E 343(ii)) and calcium dihydrogen diphosphate (E 450(vii)) used as a food additive. The measuring methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2018).
- The development of analytical methods for the determination of phosphate additives in the range of foods and beverages permitted to contain them should be considered.
- The EFSA Scientific Committee reviews current approaches to the setting of HBGVs for regulated substances which are also nutrients to assess if a coherent harmonised strategy for such risk assessments should be devised.

7. Documentation provided to EFSA

1) Application dossier for the extension of use of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338-452) in the food category 05.2 'Other confectionary including breath refreshing microsweets'. Submitted by Perfetti Van Melle SpA, April 2018.
2) CEFIC-PAPA, 2018. PAPA Contribution to EFSA request for additional information – EFSA re-evaluation of phosphates (EFSA-Q-2017-00492). Analytical data on impurities for phosphate additives used in "food for infants below 16 weeks of age. Submitted to EFSA on June 2018.
3) Mead Johnson Nutrition/Reckitt Benckiser, 2018. Submission of information to the EFSA call for technical and toxicological data on phosphates authorised as food additives in the EU (EFSA-Q-2017-00492). Submitted to EFSA on June 2018.
4) Hipp, 2018. Contribution to EFSA request for additional information – EFSA re-evaluation of phosphates (EFSA-Q-2017-00492). Submitted to EFSA June 2018.
5) Abbott Nutrition, 2018. Contribution to EFSA request for additional information – EFSA re-evaluation of phosphates. Submitted to EFSA June 2018.
6) CEFIC-PAPA, 2017. PAPA contribution to EFSA call for data – EFSA -Q-number : EFSA-Q-2017-00492. Submitted to EFSA on December 2017.
7) CEFIC-PAPA, 2018. Contribution to EFSA call for data – EFSA -Q-number: EFSA-Q-2017-00492. Submitted to EFSA on November 2018.
8) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 338 Phosphoric acid. Submitted to EFSA on August 2012.
9) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 341 Calcium phosphates. Submitted to EFSA on August 2012.
10) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 343 Magnesium phosphates. Submitted to EFSA on August 2012.
11) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 451 Triphosphates. Annex 12 on the determination of total phosphorus in cheese and cheese products by interlaboratory study. Submitted to EFSA on August 2012.
12) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 340 Potassium phosphates. Submitted to EFSA on August 2012.

13) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 339 Sodium phosphates. Submitted to EFSA on August 2012.
14) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 450 Diphosphates. Submitted to EFSA on 13 August 2012.
15) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 451 Triphosphates. Submitted to EFSA on 13 August 2012.
16) CEFIC-PAPA, 2012. Reply to EFSA: Re-evaluation of food additives: call for data (15.2.2012). E 452 Polyphosphates. Submitted to EFSA on 13 August 2012.
17) CEFIC-PAPA, 2013. Reply to EFSA: EFSA call for scientific data on miscellaneous food additives –phosphate compounds listed under the category "acidity regulators. Submitted to EFSA on 18 January 2013.
18) CEFIC-PAPA, 2014. Additional data for eight phosphates. Submitted to EFSA on 23 July 2014.
19) CEFIC-PAPA, 2016. Additional particle size data for phosphates. Submitted to EFSA on 05 February 2016.
20) BVfL, 2012. Aufruf der EFSA-052/2012 zur Neubewertung diverser in der EU zugelassener Lebensmittelzusatzstoffe unterschiedlicher Funktionsklassen im Kontext der Verordnung (EG) Nr. 1333/2008 des Europäischen Parlaments und des Rates vom 16. Dezember 2008 über Lebensmittelzusatzstoffe. Submitted to EFSA on August 2012.
21) Ludwig Maximilians Universität München, 2018. Reply to EFSA: Call for data on phosphates authorised as food additives in the EU. Submitted to EFSA on 29 January 2018.
22) ERA-EDTA, 2018. Reply to EFSA: Call for technical and toxicological data on phosphates authorised as food additives in the EU. Submitted to EFSA on 3 January 2018.
23) Dr. Paul Lohmann, 2018. Reply to EFSA: EFSA-Q-2017-00492 call for dat/E343(ii) Dimagnesium phosphate. Submitted to EFSA on 3 January 2018.
24) Renal Nutrition Group of the British Dietetic Association (BDA), 2018. Reply to EFSA: EFSA-Q-2017-00492. Submitted to EFSA on 3 January 2018.
25) Specialised Nutrition Europe (SNE), 2018. SNE submission of information to the EFSA Call for technical and toxicological data on phosphates authorised as food additives in the EU. Submitted to EFSA on 8 June 2018.
26) Pre-evaluation document "The sodium and potassium salts of phosphoric acid (E 339(i), 339(ii), 339(iii), 340(i), 340(ii) and 340(iii))" prepared by DTU Food (Contractor) 13 November 2014.
27) Pre-evaluation document "Phosphoric acid and its calcium and magnesium salts (E 338, 341(i), 341(ii), 341(iii), 343(i) and 343(ii))" prepared by DTU Food (Contractor) 13 November 2014.
28) Pre-evaluation document "Re-evaluation of disodium diphosphate (E 450(i)), trisodium diphosphate (E 450(ii)), tetrasodium diphosphate (E 450(iii)), tetrapotassium diphosphate (E 450(v)), dicalcium diphosphate (E 450(vi)) and calcium dihydrogen diphosphate (E 450(vii)) as food additives" prepared by DTU Food (Contractor) on 25 November 2013
29) Pre-evaluation document "Re-evaluation of pentasodium triphosphate and pentapotassium triphosphate (E 451) as food additives" prepared by Peter Fisk Associates Ltd on 27 November 2014.
30) Pre-evaluation document "Re-evaluation of sodium polyphosphate (E 452(i)), potassium polyphosphate (E 452(ii)), sodium calcium polyphosphate (E 452(iii)) and calcium polyphosphate (E 452(iv)) as food additives" prepared by Peter Fisk Associates Ltd 25 November 2013.
31) Association des Entreprises Produits Alimentaires Elabores (ADEPALE), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 16 November 2017.
32) Association of the European Self-Medication Industry (AESGP), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 16 November 2017.
33) Comité Européen des Fabricants de Sucre (CEFS), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 29 November 2017.

34) Dr Loges Naturheilkunde neu entdecken, 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 9 June 2017.
35) European Chemical Industry Council (CEFIC), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
36) European Dairy Association (EDA), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
37) European Fish Processors and Traders Association & European Federation of National Organisations of Importers and Exporters of Fish (AIPCE-CEP), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
38) European Potato Processors' Association (EUPPA), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
39) FDE (FoodDrinkEurope), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 29 November 2017.
40) Food Supplement Europe (FSE), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
41) IMACE, 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 29 November 2017.
42) International Chewing Gum Association (ICGA), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
43) Intersnack, 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 29 November 2017.
44) L'ALLIANCE 7, 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 30 November 2017.
45) Nathura, 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 7 March 2017.
46) Specialised Nutrition Europe (SNE), 2017. Data on use levels of phosphates (E 338-341, E 343, E 450-452) in foods in response to the EFSA call for food additives usage level and/or concentration data in food and beverages intended for human consumption (2017). Submitted to EFSA on 8 December 2017.

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Abbreviations

AAC	aortic annulus calcification
ABI	ankle brachial index
ACR	Albumin-to-creatinine ratio
ADEPALE	Association des Entreprises Produits Alimentaires Elabores
ADI	acceptable daily intake
AF	atrial fibrillation
AI	adequate intake
AIPCE-CEP	European Fish Processors and Traders Association & European Federation of National Organisations of Importers and Exporters of Fish
ALP	alkaline phosphatase
ALT	alanine aminotransferase

AMP	adenosine monophosphate
ANS	EFSA Panel on Food Additives and Nutrient Sources
AOAC	Association of Official Analytical Chemists
ARIC	Atherosclerosis Risk in Communities study
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AVC	aortic valve calcification
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
BVL	German Federal Office for Consumer Protection and Safety
bw	body weight
CAC	coronary artery calcification
CAD	coronary artery disease
cAMP	adenosine monophosphate
CARDIA	Coronary Artery Risk Development in Young Adults
CAS	Chemical Abstract Service
CE	capillary electrophoresis
CEFIC	European Chemical Industry Council
CEFS	Comité Européen des Fabricants de Sucre
cGMP	cyclic guanine monophosphate
CHD	coronary heart disease
CI	confidence interval
CIR	Cosmetic Ingredient Review Expert Panel
cITP	capillary isotachophoresis
CKD	chronic kidney disease
CRF	corticotropin-releasing factor
CTP	cytidine triphosphate
CVD	cardiovascular disease
CZE	capillary zone electrophoresis
DCP	direct current plasma spectrometry
DLS	dynamic light scattering
Dn	number-based
DRV	Dietary Reference Value
Dv	volume-based
DXA	dual X-ray absorptiometry
ECF	extracellular fluid
ECHA	European Chemicals Agency
EDA	European Dairy Association
eGFR	estimated glomerular filtration rate
EINECS	European Inventory of Existing Commercial chemical Substances
EUPPA	European Potato Processors' Association
EVM	Expert Group on Vitamins and Minerals
F_1	first-generation pups
F_2	second-generation pups
FAF	Food Additives and Flavourings
FAP	phosphates as food additives
FC	food category
FCS	food categorisation system
FDA	US Food and Drug Administration
FDE	Food Drink Europe
FDRL	Food and Drink Research Laboratories
FGF-23	*fibroblast growth factor 23*
FFQ	food frequency questionnaires
FSE	Food Supplement Europe
FSMP	food for special medical purposes
GD	gestation days

GLP	Good Laboratory Practice
GNPD	Global New Products Database
GTP	guanosine-5'-triphosphate
HBGV	health-based guidance value
HCT	hychlorothiazide
HDL	high-density lipoprotein
HF	heart failure
HPLC	high-performance liquid chromatography
HR	hazard ratio
HRT	hormone replace therapy
HTA	Hypertonia arterialis
IC	ion chromatography
ICD	International Classification of Diseases
ICGA	International Chewing Gum Association
IMT	intima-media thickness
IPCS	International Program on Chemical Safety
IQR	Interquartile Range
IUCLID	International Uniform Chemical Information Database
JECFA	Joint FAO/WHO Expert Committee on Food Additives
KCl	Potassium chloride
LC	left-censored
LD_{50}	lethal dose, 50%, i.e. dose that causes death among 50 % of treated animals
LDL	low-density lipoprotein
LOAEL	lowest-observed-adverse-effect-level
LOD	limit of detection
LOQ	limit of quantification
LVM	left ventricular mass
MB	middle-bound
MESA	Multi-Ethnic study of Atherosclerosis
MI	myocardial infarction
MPL	maximum permitted level
MTDI	maximum tolerable daily intake
NDA	Nutrition, Novel Food and Food Allergens
NHANES III	Third National Health and Nutrition Examination Survey
NMR	nuclear magnetic resonance
NOAEL	no-observable-adverse-effect level
NOEL	no-observed-effect level
NOS	Newcastle–Ottawa Scale
OECD	Organisation for Economic Co-operation and Development
OPG	osteoprotegerin
P	phosphorus
Pi	inorganic phosphorus
P_1	first-generation adults
P_2	second-generation adults
P_3	third-generation adults
PAPA	Phosphoric Acid and Phosphates Producers Association
PTH	parathyroid hormone
QICKD	Quality Improvement in Chronic Kidney Disease
QS	*quantum satis*
RANK	receptor activator of NF-kB ligand
REACH	Registration, Evaluation, Authorisation and restriction of CHemicals
RNA	ribonucleic acid
SCF	Scientific Committee for Food
SDP	plasma spectrometry
SEM	scanning electron microscopy
sFRP-4	secreted frizzled-related protein 4
SNE	Specialised Nutrition Europe

TCA	trichloroacetic acid
TD	toxicodynamics
TEM	transmission electron microscopy
TemaNord	Nordic Council of Ministers
TIA	Transient Ischemic Attack
TK	toxicokinetics
TLC	thin-layer chromatography
TmP	tubular maximum for P
TWI	tolerable weekly intake
UHT	Ultra High Temperature
UL	upper level
UTP	uridine-5'-triphosphate
UV	ultraviolet
VKM	Norwegian Scientific Committee for Food Safety
WHO	World Health Organization

Appendix A – Summary of range of phosphates functional classes according to JECFA

E No.	Phosphate name	Acidulant	Sequestrant	Synergist antioxidant	Emulsifier	Emulsion stabiliser	Texturiser	Buffer(1)	Neutralising agent	Raising agent(2)	Firming agent	Anti caking agent
338	Phosphoric acid	+	+	+								
339(i)	Monosodium		+					+				
339(ii)	Disodium				+		+	+				
339(iii)	Trisodium		+			+		+				
340(i)	Monopotassium		+					+	+	+		
340(ii)	Dipotassium		+					+		+		
340(iii)	Tripotassium		+			+		+				
341(i)	Monocalcium		+					+		+	+	
341(ii)	Dicalcium						+			+		+
341(iii)	Tricalcium							+				
343(i)	Monomagnesium							+				
343(ii)	Dimagnesium											
450(i)	Disodium di		+						+	+		
450(ii)	Trisodium di				+	+				+		
450(iii)	Tetrasodium di		+		+			+				
450(v)	Tetrapotassium di				+		+					
450(vi)	Dicalcium di							+	+	+		
450(vii)	Calcium dihydrogen				+	+				+		
450(ix)	Magnesium dihydrogen	+				+				+		
451(i)	Pentasodium tri		+				+					
451(ii)	Pentapotassium tri						+					
452(i)	Sodium poly		+		+		+					
452(ii)	Potassium poly		+		+		+					
452(iii)	Sodium calcium poly				+	+				+		
452(iv)	Calcium poly		+		+		+					

(1): Including acidity regulator.
(2): Including leavening agent/dough conditioner/yeast food.

Appendix B – Table for converting phosphates into phosphorus pentoxide (P2O5) and phosphorus (P)

E number	Formula	MW	1 g substance = g P_2O_5	1 g P_2O_5 = g P
E 338	H_3PO_4	98.00	0.724	0.315
E 339(i)	NaH_2PO_4	119.98	0.592	0.258
"	NaH_2PO_4, H_2O	138.00	0.514	0.224
"	NaH_2PO_4, $2H_2O$	156.01	0.455	0.198
E 339(ii)	Na_2HPO_4	141.96	0.500	0.218
"	Na_2HPO_4, $2H_2O$	177.99	0.399	0.174
"	Na_2HPO_4, $7H_2O$	268.06	0.265	0.115
"	Na_2HPO_4, $12H_2O$	358.14	0.198	0.086
E 339(iii)	Na_3PO_4	163.94	0.433	0.188
"	Na_3PO_4, $2H_2O$	181.96	0.390	0.170
"	Na_3PO_4, $12H_2O$	380.12	0.187	0.081
E 340(i)	KH_2PO_4	136.09	0.522	0.227
E 340(ii)	$K_2H_2PO_4$	174.17	0.407	0.177
E 340(iii)	K_3PO_4	212.28	0.334	0.145
E 341(i)	$Ca(H_2PO_4)_2$	234.05	0.606	0.264
E 341(ii)	CaH_2PO_4, $2H_2O$	172.09	0.412	0.179
E 341(iii)	10CaO, $3P_2O_5$, H_2O	1,004.67	0.424	0.185
E 343(i)	$Mg(H_2PO_4)2$, $4H_2O$	290.34	0.489	0.213
E 343(ii)	$MgHPO_4$, n H_2O (n = 0–3)	120.28*	0.590	0.257
E450(i)	$Na_2H_2P_2O_7$	221.94	0.640	0.279
E450(ii)	$Na_3HP_2O_7$	243.92	0.582	0.253
"	$Na_3HP_2O_7$, H_2O	261.94	0.542	0.236
E 450(iii)	$Na_4P_2O_7$	265.90	0.534	0.233
"	$Na_4P_2O_7$, $10H_2O$	446.05	0.318	0.138
E 450(v)	$K_4P_2O_7$	330.34	0.430	0.187
"	$K_4P_2O_7$, $3H_2O$	383.39	0.369	0.161
E 450(vi)	$Ca_2P_2O_7$	254.10	0.559	0.243
E 450(vii)	$CaH_2P_2O_7$	216.04	0.657	0.286
E 451(i)	$Na_5P_3O_{10}$	367.86	0.579	0.252
"	$Na_5P_3O_{10}$, $6H_2O$	475.95	0.447	0.195
E 451(ii)	$K_5P_3O_{10}$	448.41	0.475	0.207

E number	Formula	MW	1 g substance = g P_2O_5	1 g P_2O_5 = g P
E 452(i)	$(NaPO_3)_n$ (n > 3)	102*n	0.696*n	0.303*n
E 452(ii)	$(KPO_3)_n$	118*n	0.601*n	0.262*n
E 452(iv)	$(CaP_2O_6)_n$ (n ≥ 2)	198*n	0.717*n	0.312*n

*: Anhydrous form.

Appendix C – The link between phosphates and cardiovascular diseases: epidemiology search protocol

Objective

To assess, if any, the association between phosphates/phosphorus intake and cardiovascular diseases and serum phosphorus level and cardiovascular diseases, including cardiovascular specific mortality.

To assess, if any, the association between phosphates/phosphorus intake and stroke and serum phosphorus level and stroke, including stroke specific mortality.

To assess, if any, the association between phosphates intake and serum phosphorus levels and intermediate outcomes of cardiovascular events, such as coronary artery calcification.

To assess, if any, the association between phosphate-responsive hormones (fibroblast growth factor-23, parathyroid hormone) and cardiovascular diseases and/or stroke.

Methods

Types of studies and participants

Observational studies (cohort, case–control and cross-sectional studies) will be included, that investigated the association between: phosphates in diet and/or serum phosphorus and cardiovascular diseases; phosphates in diet and/or serum phosphorus and stroke; phosphates in diet and/or serum phosphorus and cardiovascular specific mortality; phosphates in diet and/or serum phosphorus and stroke specific mortality; phosphates in diet and serum phosphorus levels and intermediate outcomes of cardiovascular events such as coronary artery calcification; phosphate-responsive hormones (fibroblast growth factor-23, parathyroid hormone) and cardiovascular events.

Study participants will be adults of either sex or age. Studies that evaluated phosphates/phosphorus from other sources other than diet (medicine, environmental/occupational exposure) will be excluded. Studies that were included in the EFSA report (2013) that are considered informative will be also included in the report.

Types of outcome measures to be included

Primary outcome:

Incidence of cardiovascular diseases and incidence of stroke.

Secondary outcome:

(i) Intermediate outcomes for cardiovascular diseases and cardiovascular mortality.
(ii) Phosphate-responsive hormones (fibroblast growth factor-23, parathyroid hormone and calcitriol) and cardiovascular events.

Search Strategy and Data Extraction

Electronic searches

Relevant studies were located by searching PubMed. PRISMA flow diagram (Moher et al., 2009) helped managing search strategy and data extraction.

((“phosphates”[MeSH Terms] OR “phosphates”[All Fields] OR “phosphate”[All Fields]) AND intake [All Fields]) AND (“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields]) AND (“epidemiology”[Subheading] OR “epidemiology”[All Fields] OR “epidemiology”[MeSH Terms])

AND

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AND

(“phosphates”[MeSH Terms] OR “phosphates”[All Fields]) AND (“atherosclerosis”[MeSH Terms] OR “atherosclerosis”[All Fields] OR “atherogenesis”[All Fields]) AND (“cohort studies”[MeSH Terms] OR (“cohort”[All Fields] AND “studies”[All Fields]) OR “cohort studies”[All Fields] OR “cohort”[All Fields])

AND

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AND

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AND

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AND

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AND

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AND

("parathyroid hormone"[MeSH Terms] OR ("parathyroid"[All Fields] AND "hormone"[All Fields]) OR "parathyroid hormone"[All Fields]) AND ("phosphates"[MeSH Terms] OR "phosphates"[All Fields]) AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("case-control studies"[MeSH Terms] OR ("case-control"[All Fields] AND "studies"[All Fields]) OR "case-control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields]) OR "case control"[All Fields])

AND

("fibroblast growth factors"[MeSH Terms] OR ("fibroblast"[All Fields] AND "growth"[All Fields] AND "factors"[All Fields]) OR "fibroblast growth factors"[All Fields] OR ("fibroblast"[All Fields] AND "growth"[All Fields] AND "factor"[All Fields]) OR "fibroblast growth factor"[All Fields]) AND ("phosphates"[MeSH Terms] OR "phosphates"[All Fields]) AND ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields])

AND

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AND "studies"[All Fields]) OR "case-control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields]) OR "case control"[All Fields])

No language restriction was applied. Previous review articles will be hand searched for other relevant studies.

Study selection, data extraction and assessment of methodology quality (bias)

Working Group experts in epidemiology will identify potential studies to be added in the draft review provided by EFSA. These experts will screen the full-texts and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. Disagreement will be solved through discussion or, if required, the working group will be consulted. Duplicate records will be identified and excluded and multiple reports that relate to the same study will collated so that each study rather than each report is the unit of interest in the evaluation.

Sources of bias in observational studies can be due to the study design and analytic methods. Using statistical adjustments in the models or matching procedures, may decrease the risk of bias, which can increase confidence in the results. The Newcastle–Ottawa Scale (NOS) will be used as a guideline for describing and interpreting studies. The latter scale for judging the quality of the studies will be used if a meta-analysis is envisaged, as recommended by the Cochrane Collaboration (Higgins et al., 2008). This scale uses a star system to assess the quality of a study in three domains: selection, comparability and outcome (cohort studies) or exposure (case–control studies). The NOS assigns a maximum of four stars for selection, two stars for comparability and three stars for exposure/outcome. Therefore, nine stars reflect the highest quality. Any discrepancies will be addressed by a joint re-evaluation of the original article by the epidemiology group. Studies in which mortality/and intermediate outcomes are the outcome will be given a different weight. Cross-sectional studies are of limited value in assessing whether there is a true exposure-outcome relationship, nonetheless they will be described in the opinion for completeness.

The following items will be included while describing each study:

1) Type of study (case–control/cohort/cross-sectional)
2) Characteristics of the population and setting (e.g. age, sex, sample size, sources and methods of selection of participants, eligibility criteria, methods of case ascertainment and control selection, matching criteria and the number of controls per case)
3) Objective of the study
4) Exposure (e.g. type of dietary questionnaire and mode of assessment)
5) Type of outcome (incidence/mortality/intermediate outcomes)
6) Number of cases identified during the follow-up (cohort)
7) Time of follow-up and number of lost to follow-up
8) Results of the main findings:
    - 8.1) ORs or hazard ratios, with their 95% confidence intervals and p for trend if present and cut-off values associated with the risk of cardiovascular diseases and/or stroke and/or intermediate outcomes and/or cardiovascular and/or stroke mortality
    - 8.2) Confounding factors considered by the authors (main risk factors for the specific outcomes) and included in the multivariate analysis (e.g. age, sex, socioeconomic status and/or education, smoking, BMI, calcium, alcohol, vitamin D, total energy intake)
9) Subgroup analysis if conducted (e.g. sex and factors that may potentially affect phosphorus' metabolism such as renal dysfunction)
10) Strength and limitation of each study.

Appendix D – The link between phosphates, bone metabolism and osteoporosis: epidemiology search protocol

Search 1

Database	Coverage	Access
Embase	Inception-present	www.embase.com
Pubmed	Inception-present	www.ncbi.nlm.nih.gov/pubmed

Search strategies

Embase

No.	Query
#13	#11 NOT #12
#12	'osteoporosis'/exp OR osteoporosis:ti,ab
#11	#10 AND ([english]/lim OR [german]/lim)
#10	#8 NOT #9
#9	('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp
#8	#1 AND #7
#7	#2 OR #3 OR #4 OR #5 OR #6
#6	(broken NEAR/5 bone*):ti,ab
#5	fracture*:ti,ab OR bmc:ti,ab OR bmd:ti,ab
#4	bone*:ti,ab AND mineral:ti,ab AND concentration:ti,ab
#3	(bone* NEAR/5 (content OR densit* OR health OR mass OR volume OR loss* OR metabolism OR mineral* OR disease*)):ti,ab
#2	'bone health'/exp OR 'bone density'/exp OR 'bone disease'/de OR 'bone mass'/exp OR 'bone mineral'/exp OR 'fracture'/exp OR 'bone metabolism'/exp
#1	'phosphate'/exp AND 'dietary intake'/de OR (((phosphate OR phosphates) NEAR/15 intak*):ti,ab)

PubMed

No.	Query
#13	#11 NOT #12
#12	'osteoporosis'/exp OR osteoporosis:ti,ab
#11	#10 AND ([english]/lim OR [german]/lim)
#10	#8 NOT #9
#9	('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp
#8	#1 AND #7
#7	#2 OR #3 OR #4 OR #5 OR #6
#6	(broken NEAR/5 bone*):ti,ab
#5	fracture*:ti,ab OR bmc:ti,ab OR bmd:ti,ab
#4	bone*:ti,ab AND mineral:ti,ab AND concentration:ti,ab
#3	(bone* NEAR/5 (content OR densit* OR health OR mass OR volume OR loss* OR metabolism OR mineral* OR disease*)):ti,ab
#2	'bone health'/exp OR 'bone density'/exp OR 'bone disease'/de OR 'bone mass'/exp OR 'bone mineral'/exp OR 'fracture'/exp OR 'bone metabolism'/exp
#1	'phosphate'/exp AND 'dietary intake'/de OR (((phosphate OR phosphates) NEAR/15 intak*):ti,ab)

Search 2

("phosphates"[MeSH Terms] OR "phosphates"[All Fields]) AND (("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]))

("phosphates"[MeSH Terms] OR "phosphates"[All Fields]) AND (("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields])

AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields]))

(("phosphorus, dietary"[MeSH Terms] OR ("phosphorus"[All Fields] AND "dietary"[All Fields]) OR "dietary phosphorus"[All Fields] OR "phosphorus"[All Fields] OR "phosphorus"[MeSH Terms]) AND intake[All Fields]) AND (("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields]))

("phosphorus, dietary"[MeSH Terms] OR ("phosphorus"[All Fields] AND "dietary"[All Fields]) OR "dietary phosphorus"[All Fields] OR "phosphorus"[All Fields] OR "phosphorus"[MeSH Terms]) AND ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("case-control studies"[MeSH Terms] OR ("case-control"[All Fields] AND "studies"[All Fields]) OR "case-control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields] AND "study"[All Fields]) OR "case control study"[All Fields])

Phosphate [All Fields] AND ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("case-control studies"[MeSH Terms] OR ("case-control"[All Fields] AND "studies"[All Fields]) OR "case-control studies"[All Fields] OR ("case"[All Fields] AND "control"[All Fields] AND "study"[All Fields]) OR "case control study"[All Fields])

("phosphoric acid"[Supplementary Concept] OR "phosphoric acid"[All Fields] OR "phosphoric acids"[MeSH Terms] OR ("phosphoric"[All Fields] AND "acids"[All Fields]) OR "phosphoric acids"[All Fields] OR ("phosphoric"[All Fields] AND "acid"[All Fields])) AND ("fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fractures"[All Fields]) AND ("cohort studies"[MeSH Terms] OR ("cohort"[All Fields] AND "studies"[All Fields]) OR "cohort studies"[All Fields] OR "cohort"[All Fields])

Appendix E – Identity of the substances and specifications

Phosphoric acid

According to Commission Regulation (EU) No 231/2012, the food additive E 338 is identified as
Chemical name: Phosphoric acid
EINECS Number: 231-633-2
Chemical formula: H_3PO_4
Molecular weight: 98.00
Physical description: Clear, colourless, odourless, viscous liquid
CAS number: 7664-38-20
Solubility: Miscible with water and with ethanol

Phosphoric acid has a melting point of 42.4°C and a boiling point of 407°C (CRC, 2012a). Regarding acidity, the dissociation constants are pKa1 2.12, pKa2 7.21 and pKa3 12.67 (EFSA-FEEDAP-Panel, 2013). The partition coefficient (log p value) is −1.644 ± 0.350 (at a temperature of 25°C) (Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2013 ACD/Labs) (SciFinder, 2013a).

Synonyms include: Orthophosphoric acid and monophosphoric acid.

Monosodium phosphate

According to Commission Regulation (EU) No 231/2012[20]), the food additive E 339(i) is identified as
Chemical name: Sodium dihydrogen monophosphate
EINECS Number: 231-449-2
Chemical formula: NaH_2PO_4 (anhydrous form), $NaH_2PO_4 \cdot H_2O$ (monohydrate form) or $NaH_2PO_4 \cdot 2H_2O$ (dehydrate form)
Molecular weight: 119.98 (anhydrous form), 138.00 (monohydrate form) or 156.01 (dehydrate form)
Physical description: White odourless, slightly deliquescent powder, crystals or granules
CAS number: 7558-80-7
Solubility: Freely soluble in water and insoluble in ethanol or ether

Monosodium phosphate (anhydrous) has a melting point of 200°C, at which temperature it decomposes (CRC, 2012a).

No information on log p value has been retrieved.

Synonyms include: Monosodium monophosphate; acid monosodium monophosphate; monosodium orthophosphate; monobasic sodium phosphate and sodium dihydrogen monophosphate.

Disodium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 339(ii) is identified as
Chemical name: Disodium hydrogen monophosphate and disodium hydrogen orthophosphate
EINECS Number: 231-448-7
Chemical formula: $Na_2H_2PO_4$ (anhydrous form), $Na_2H_2PO_4 \cdot nH_2O$ (n = 2,7 or 12) (hydrates form)
Molecular weight: 141.98 (anhydrous form)

Physical description: Anhydrous disodium phosphate occurs as a white, hygroscopic, odourless powder. The dihydrate occurs as a white crystalline, odourless solid. The heptahydrate occurs as white, odourless, efflorescent crystals or granular powder. The dodecahydrate occurs as a white, efflorescent, odourless powder or crystals

CAS number: 7558-79-4
Solubility: Disodium phosphate is freely soluble in water and insoluble in ethanol

No information on melting point or log p value has been retrieved.

Synonyms include: Disodium monophosphate; secondary sodium phosphate; disodium orthophosphate; dibasic sodium phosphate and disodium acid phosphate.

Trisodium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 339(iii) is identified as
Chemical name: Trisodium monophosphate, trisodium phosphate and trisodium orthophosphate
EINECS Number: 231-509-8

[20] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83, 22.3.2012, p. 1–295.

Chemical formula: Na_3PO_4 (anhydrous form), $Na_3PO_4 \cdot nH_2O$ (n = 1/2,1,6,8 or 12) (hydrates form)
Molecular weight: 163.94 (anhydrous form)
Physical description: White odourless crystals, granules or a crystalline powder
CAS number: 7601-54-9
Solubility|: Freely soluble in water and insoluble in ethanol
Trisodium phosphate (anhydrous) has a melting point of 1,583°C (CRC, 2012b).
No information on log p value has been retrieved.
Synonyms include: Tribasic sodium phosphate and sodium phosphate.

Monopotassium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 340(i) is identified as
Chemical name: Potassium dihydrogen phosphate, monopotassium dihydrogen orthophosphate and monopotassium dihydrogen monophosphate
EINECS Number: 231-913-4
Chemical formula: KH_2PO_4
Molecular weight: 136.09
Physical description: Odourless, colourless crystals or a white granular or crystalline powder
CAS number: 7778-77-0
Solubility: Freely soluble in water and insoluble in ethanol
Monopotassium phosphate has a melting point of 253°C (CRC, 2012e; SciFinder, 2013c).
No information on log p value has been retrieved.
Synonyms include: Monobasic potassium phosphate; monopotassium monophosphate and mono potassium orthophosphate.

Dipotassium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 340(ii) is identified as
Chemical name: Dipotassium hydrogen monophosphate, dipotassium hydrogen phosphate and dipotassium hydrogen orthophosphate
EINECS Number: 231-834-5
Chemical formula: K_2HPO_4
Molecular weight: 174.18
Physical description: Colourless or white granular powder, crystals or masses and is a deliquescent and hygroscopic substance
CAS number: 7758-11-4
Solubility: Freely soluble in water and insoluble in ethanol
Dipotassium phosphate has a melting point of 151.5–154.0°C where it decomposes (CRC, 2012c).
No information on log p value has been retrieved.
Synonyms include: Dipotassium monophosphate; secondary potassium phosphate; dipotassium orthophospahte and dibasic potassium phosphate.

Tripotassium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 340(i) is identified as
Chemical name: Tripotassium monophosphate, tripotassium phosphate and tripotassium orthophosphate
EINECS Number: 231-907-1
Chemical formula: K_3PO_4 (anhydrous form), $K_3PO_4 \cdot nH_2O$ (n = 1 or 3) (hydrates form)
Molecular weight: 212.27 (anhydrous form)
Physical description: Colourless or white, odourless hygroscopic crystals or granules
CAS number: 7778-53-2
Solubility: Freely soluble in water and insoluble in ethanol
Tripotassium phosphate (anhydrous) has a melting point of 1,340°C (CRC, 2012d).
No information on log p value has been retrieved.
Synonyms include: Tribasic potassium phosphate; potassium phosphate and tripotassium orthophosphate.

Calcium dihydrogen phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 341 (i) is identified as
Chemical name: Calcium dihydrogen phosphate
EINECS Number: 231-837-1

Chemical formula: $Ca(H_2PO_4)_2$ anhydrous or $Ca(H_2PO_4)_2 \cdot H_2O$ monohydrate
Molecular weight: Anhydrous 234.05; monohydrate 252.07
Physical description: Hygroscopic white crystals or granules or granular powder
CAS number: anhydrous 7758-23-8; monohydrate 10031-30-8
Solubility: Sparingly soluble in water, insoluble in ethanol
Calcium dihydrogen phosphate monohydrate has a melting point of 100°C where it decomposes (CRC, 2012d).
No information on log p value has been retrieved.
Synonyms include: Monobasic calcium phosphate; monocalcium orthophosphate; monocalcium phosphate; calcium biphosphate and acid calcium phosphate.

Calcium hydrogen phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 341(ii) is identified as
Chemical name: Calcium monohydrogen phosphate, calcium hydrogen orthophosphate and secondary calcium phosphate
EINECS Number: 231-826-1
Chemical formula: $CaHPO_4$ anhydrous or $Ca(HPO_4) \cdot 2H_2O$ dihydrate
Molecular weight: anhydrous 136.06; dihydrate 172.09
Physical description: Hygroscopic white crystals or granules or granular powder
CAS number: anhydrous 7757-9309
Solubility: Sparingly soluble in water, insoluble in ethanol
No information on melting point or log p value has been retrieved.
Synonyms include: Dibasic calcium phosphate and dicalcium phosphate

Tricalcium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 341(iii) is identified as
Chemical name: Pentacalcium hydroxy monophosphate and tricalcium monophosphate
EINECS Number: 235-330-6
Chemical formula: $Ca_5(PO_4)_3 \cdot OH$ or $Ca_3(PO_4)_2$
Molecular weight: 502 $Ca_5(PO_4)_3$; 310 $Ca_3(PO_4)_2$
Physical description: White, odourless powder which is stable in air
CAS number: 7758-87-4
Solubility: Practically insoluble in water; insoluble in ethanol, soluble in dilute hydrochloric and nitric acid
Tricalcium phosphate has a melting point of 1,670°C (CRC, 2012c; SciFinder, 2013b).
No information on log p value has been retrieved.
Synonyms include: Calcium phosphate, tribasic; calcium orthophosphate; pentacalcium hydroxy monophosphate and calcium hydroxyapatite.

Monomagnesium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 343(i) is identified as
Chemical name: Monomagnesium dihydrogen monophosphate
EINECS Number: 236-004-6
Chemical formula: $Mg(H_2PO_4)_2 \cdot nH_2O$ (n = 0–4)
Molecular weight: 218.3 (anhydrous), 254.3 (dihydrate), 290.3 (tetrahydrate)
Physical description: White, odourless, crystalline powder
CAS number: 13092-66-5 (anhydrous),15609-87-7 (dehydrate)
Solubility: Slightly soluble in water
No information on melting point or log p value has been retrieved.
Synonyms include: Magnesium dihydrogen phosphate; magnesium phosphate, monobasic; monomagnesium orthophosphate.

Dimagnesium phosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 343(ii) is identified as
Chemical name: dimagnesium monohydrogen monophosphate
EINECS Number: 231-823-5
Chemical formula: $MgHPO_4 \cdot nH_2O$ (n = 0–3)
Molecular weight: 120.30 (anhydrous)
Physical description: white, odourless, crystalline powder

CAS number: 7757-86-0
Solubility: Slightly soluble in water, soluble in dilute acids, but insoluble in ethanol
Dimagnesium phosphate has a melting point of 550°C where it decomposes (CRC, 2012b).
No information on log p value has been retrieved.
Synonyms include: Magnesium hydrogen phosphate; magnesium phosphate, dibasic; dimagnesium orthophosphate and secondary magnesium phosphate.

Disodium diphosphate

According to Commission Regulation (EU) No 231/2012[20]), the food additive E 450(i) is identified as
Chemical name: Disodium dihydrogen diphosphate
EINECS Number: 231-972-6
Chemical formula: $Na_2H_2P_2O_7$
Molecular weight: 221.94
Physical description: White powder or grains
CAS number: 7758-16-9
Solubility: Soluble in water
The melting point is reported as > 450°C (Haynes, 2010).
Synonyms include: disodium dihydrogen diphosphate, disodium pyrophosphate, disodium dihydrogen pyrophosphate and acid sodium pyrophosphate.

Trisodium diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(ii) is identified as
Chemical name:
EINECS Number: 238-735-6
Chemical formula: $Na_3HP_2O_7$ (anhydrous form) or $Na_3HP_2O_7 \cdot H_2O$ (monohydrate form)
Molecular weight: 243.93 (anhydrous form), 261.95 (monohydrate form)
Physical description: White powder or grains
CAS number: 14691-80-6 (anhydrous form), 26573-04-6 (monohydrate form)
Solubility: Soluble in water
Synonyms include: trisodium monohydrogen diphosphate, trisodium monohydrogen pyrophosphate, trisodium hydrogen phosphate, trisodium pyrophosphate and acid trisodium pyrophosphate.

Tetrasodium diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(iii) is identified as
Chemical name: Tetrasodium phosphate
EINECS Number: 231-767-1
Chemical formula: $Na_4P_2O_7$ (anhydrous form) or $Na_4P_2O_7 \cdot 10H_2O$ (decahydrate form)
Molecular weight: 265.94 (anhydrous form), 446.09 (decahydrate form)
Physical description: Colourless or white crystals or a white crystalline or granular powder
CAS number: 7722-88-5
Solubility: Soluble in water
The melting point is reported as 988°C (Haynes, 2010).
Synonyms include: include tetrasodium pyrophosphate, tetrasodium disphosphate, tetrasodium phosphate and sodium pyrophosphate.

Tetrapotassium diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(v) is identified as
Chemical name: Tetrapotassium diphosphate
EINECS Number: 230-785-7
Chemical formula: $K_4P_2O_7$
Molecular weight: 330.34 (anhydrous form)
Physical description: Colourless crystals or a white, very hygroscopic powder
CAS number: 7320-34-5
Solubility: Soluble in water
The substance is reported to decompose at 1,300°C (Haynes, 2010).
Synonyms include: Tetrapotassium pyrophosphate, potassium pyrophosphate and tetrapotassium salt of diphosphoric acid.

Dicalcium diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(vi) is identified as
Chemical name: Dicalcium diphosphate, dicalcium pyrophosphate
EINECS Number: 232-221-5
Chemical formula: $Ca_2P_2O_7$
Molecular weight: 254.12
Physical description: Fine, white, odourless powder
CAS number: 7790-76-3
Solubility: Insoluble in water
Synonyms include: Calcium pyrophosphate and dicalcium pyrophosphate.

Calcium dihydrogen diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(vii) is identified as
Chemical name: Calcium dihydrogen diphosphate
EINECS Number: 238-933-3
Chemical formula: $CaH_2P_2O_7$
Molecular weight: 215.97
Physical description: White crystals or powder
CAS number: 14866-19-4
Solubility: Not specified in Commission Regulation (EU) No 231/2012
Synonyms include: Acid calcium pyrophosphate, monocalcium dihydrogen pyrophosphate, calcium dihydrogen pyrophosphate and monocalcium dihydrogen diphosphate.

Magnesium dihydrogen diphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 450(ix) is identified as
Chemical name: Monomagnesium dihydrogen diphosphate
EINECS Number: 244-016-8
Chemical formula: $MgH_2P_2O_7$
Molecular weight: 200.25
Physical description: White crystals or powder
CAS number: 13446-24-7
Solubility: Slightly soluble in water, practically insoluble in ethanol
Synonyms include: Acid magnesium pyrophosphate, monomagnesium dihydrogen pyrophosphate; magnesium diphosphate, magnesium pyrophosphate.

Pentasodium triphosphate

According to Commission Regulation (EU) No 231/2012[20]), the food additive E 451(i) is identified as
Chemical name: Pentasodium triphosphate
EINECS Number: 231-838-7
Chemical formula: $Na_5P_3O_{10} \cdot nH_2O$ (n = 0 or 6)
Molecular weight: 367.86 (anhydrous form), 475.94 (hexahydrate form)
Physical description: White, slightly hygroscopic granules or powder
CAS number: 7758-29-4
Solubility: Freely soluble in water and insoluble in ethanol
The melting point is reported as 622°C (Haynes, 2010).
Synonyms include: pentasodium tripolyphosphate and sodium tripolyphosphate.

Pentapotassium triphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 451(ii) is identified as
Chemical name: Pentapotassium triphosphate, pentapotassium tripolyphosphate
EINECS Number: 237-574-9
Chemical formula: $K_5P_3O_{10}$
Molecular weight: 448.82
Physical description: White, very hygroscopic powder or granules
CAS number: 13845-36-8
Solubility: Very soluble in water
Synonyms include: potassium triphosphate and potassium tripolyphosphate.

Sodium polyphosphate

According to Commission Regulation (EU) No 231/2012[20]), the food additive E 452(i) is identified as
Chemical name: Sodium polyphosphate
Commission Regulation (EU) No 231/2012 is laying down specifications for E 452(i), in two forms.

Soluble sodium polyphosphate

EINECS Number: 272-808-3
Chemical formula: $H_{(n+2)}P_nO_{(3n+1)}$ where 'n' is not less than 2
Molecular weight: $(102)_n$
Physical description: Colourless or white, transparent platelets, granules or powders
CAS number: 68915-31-1, 10124-56-8 and 10362-03-2
Solubility: Very soluble in water
Synonyms include: sodium hexametaphosphate; sodium tetrapolyphosphate; Graham's salt; sodium polyphosphates, glassy; sodium polymetaphosphate; sodium metaphosphate.
Soluble sodium polyphosphate is described in Commission Regulation (EU) No 231/2012 as follows:

'Soluble sodium polyphosphates are obtained by fusion and subsequent chilling of sodium orthophosphates. These compounds are a class consisting of several amorphous, water-soluble polyphosphates composed of linear chains of metaphosphate units, $(NaPO_3)_x$ where $x \geq 2$, terminated by Na_2PO_4 groups. These substances are usually identified by their Na_2O/P_2O_5 ratio or their P_2O_5 content. The Na_2O/P_2O_5 ratios vary from about 1.3 for sodium tetrapolyphosphate, where x = approximately 4; to about 1.1 for Graham's salt, commonly called sodium hexametaphosphate, where x = 13 to 18; and to about 1.0 for the higher molecular weight sodium polyphosphates, where x = 20 to 100 or more. The pH of their solutions varies from 3.0 to 9.0'.

JECFA specification describes the chain structure as 'metaphosphate units, $(NaPO_3)_x$ where $x = 2$'; this is at odds with this point in the definition above and also with the comments in JECFA on the composition of various forms, which are the same as those in the definition above.

The REACH Registration Dossier on sodium metaphosphate (REACH Registration Dossier, online) submitted to the European Chemicals Agency (ECHA) includes a melting point of > 723 K, and a solubility of 54.8–59.7% (w/w).

Insoluble sodium polyphosphate

EINECS Number: 272-808-3
Chemical formula: $H_{(n+2)}P_nO_{(3n+1)}$ where 'n' is not less than 2
Molecular weight: $(102)_n$
Physical description: A white crystalline powder
CAS number: No CAS registry number is included in Commission Regulation (EU) No 231/2012 for this form
Solubility: Insoluble in water, soluble in mineral acids and in solutions of potassium and ammonium (but not sodium) chlorides
Synonyms include: Insoluble sodium metaphosphate; Maddrell's salt; insoluble sodium polyphosphate; IMP
This form of sodium polyphosphate is not included in the JECFA specifications.

Potassium polyphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 452 (ii) is identified as
Chemical name: Potassium polyphosphate
EINECS Number: 232-212-6
Chemical formula: $(KPO_3)_n$
Molecular weight: $(102)_n$
Physical description: Fine white powder or crystals or colourless glassy platelets
CAS number: 7790-53-6
Synonyms include: One gram dissolves in 100 mL of a 1 in 25 solution of sodium acetate
Synonyms include: Include potassium metaphosphate, potassium polymetaphosphate and Kurrol salt.

Sodium calcium polyphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 452 (iii) is identified as

Chemical name: sodium calcium polyphosphate

EINECS Number: 233-782-9[21]

Chemical formula: $(NaPO_3)_n$ CaO where n is typically 5

Molecular weight: No molecular weight is included in Commission Regulation (EU) No 231/2012 and in JECFA specifications

Physical description: White glassy crystals or spheres

CAS number: No CAS registry number is included in either Commission Regulation (EU) No 231/2012 or the JECFA specifications for this substance.

Solubility: Not included in either Commission Regulation (EU) No 231/2012 or the JECFA specifications for this substance

Synonyms include: Sodium calcium polyphosphate, glassy.

Calcium polyphosphate

According to Commission Regulation (EU) No 231/2012, the food additive E 452 (iv) is identified as

Chemical name: calcium polyphosphate

EINECS Number: 236-769-6

Chemical formula: $(CaP_2O_6)_n$

Molecular weight: $(198)_n$

Physical description: Odourless, colourless crystals or white powder

CAS number: No CAS registry number is included in either Commission Regulation (EU) No 231/2012 or the JECFA specifications for this substance, entering the EINECS number in the ESIS database and the ECHA public database gives a CAS registry number of 13477-39-9

Solubility: Usually sparingly soluble in water, soluble in acid medium

Synonyms include: Calcium metaphosphate and calcium polymetaphosphate.

The specifications for phosphoric acid (E 338), monocalcium phosphate (E 341(i)), dicalcium phosphate (E 341(ii)), tricalcium phosphate (E 341(iii)), monomagnesium phosphate (E 343(i)), dimagnesium phosphate (E 343(ii)) monosodium phosphate (E 339(i)), disodium phosphate (E 339(ii)), trisodium phosphate (E 339(iii)), monopotassium phosphate (E 340(i)), dipotassium phosphate (E 340(ii)), tripotassium phosphate (E 340(iii)), disodium diphosphate (E 450(i)), trisodium diphosphate (E 450(ii)), tetrasodium diphosphate (E 450(iii)), tetrapotassium diphosphate (E 450(v)), dicalcium diphosphate (E 450(vi)), calcium dihydrogen diphosphate (E 450(vii)), pentasodium triphosphate (E 451(i)), pentapotassium triphosphate (E 451(ii)), sodium polyphosphate (E 452(i)), potassium polyphosphate (E 452(ii)), sodium calcium polyphosphate (E 452(iii)) and calcium polyphosphate (E 452(iv)) as defined in the Commission Regulation (EU) No 231/2012 and by JECFA are listed in Tables E.1–E.26.

[21] There is a lack of clarity in relation to the EINECS number. Entering 233-782-9 into the ESIS database or the ECHA public database returns the substance sodium metaphosphate with a CAS registry number 10361-03-2; this name and number are included under sodium polyphosphate I: soluble polyphosphate in Commission Regulation (EU) No 231/2012 and the number is included in the JECFA specification for INS No. 452(i). The same name and/or CAS registry number are associated with EINECS number 233-782-9 on some chemical supplier web-sites, for example Guidechem (http://www.guidechem.com/products/10361-03-2.html), Carlo Erba (http://www.carloerbareagenti.com/Repository/DIR199/CH1213_GB.pdf).

Table E.1: Specifications for phosphoric acid (E 338) according to Commission Regulation (EU) No 231/2012 and JECFA (2002)

	Commission Regulation (EU) No 231/2012	JECFA (2002)
Definition	Phosphoric acid	Phosphoric acid, orthophosphoric acid
Assay	Content not less than 67.0% and not more than 85.7%. Phosphoric acid is commercially available as an aqueous solution at variable concentrations	Not less than 75% and not less than the minimum or within the range of percent claimed by the vendor
Description	Clear, colourless, viscous liquid	Clear, colourless, odourless, viscous liquid
Identification	Test for acid: Passes test Test for phosphate: Passes test	Solubility: Miscible with water and with ethanol Test for acid: Strongly acid, even at high dilution Test for phosphate: Neutralise a few millilitres of phosphoric acid and add dilute nitric acid TS. Then, add an equal volume of ammonium molybdate TS and warm. A bright canary-yellow precipitate is obtained which is soluble in dilute ammonia TS
Purity[(a)]	Volatile acids: not more than 10 mg/kg (as acetic acid) Chlorides: not more than 200 mg/kg (expressed as chlorine) Nitrates: not more than 5 mg/kg (as $NaNO_3$) Sulfates: not more than 1,500 mg/kg (as $CaSO_4$) Fluoride: not more than 10 mg/kg (expressed as fluorine) Arsenic: not more than 1 mg/kg Cadmium: not more than 1 mg/kg Lead: not more than 1 mg/kg Mercury: not more than 1 mg/kg	Nitrates: not more than 5 mg/kg Volatile acids: not more than 10 mg/kg as acetic acid Chlorides (Vol. 4): not more than 200 mg/kg as chlorine Sulfates (Vol. 4): not more than 0.15% Fluoride (Vol. 4): not more than 10 mg/kg Arsenic (Vol. 4): not more than 3 mg/kg Lead (Vol. 4): not more than 4 mg/kg

(a): This specification refers to a 75% aqueous solution.

Table E.2: Specifications for monosodium phosphate (E 339(i)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006b,c,d,e,f)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	After drying at 60°C for 1 h and then at 105°C for 4 h, contains not less than 97% of NaH_2PO_4 P_2O_5 content between 58.0% and 60.0% on the anhydrous basis	Not less than 97% after drying
Description	A white odourless, slightly deliquescent powder, crystals or granules	White odourless, slightly deliquescent powder, crystals, or granules
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Freely soluble in water. Insoluble in ethanol or ether	Freely soluble in water; insoluble in ethanol, ether or chloroform
pH	Between 4.1 and 5.0 (1% solution)	4.2–4.6 (1 in 100 solution)
Test for orthophosphate	–	To a 1% solution of the sample add silver nitrate TS; the yellow precipitate formed is soluble in dilute nitric acid TS

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Purity		
Loss on drying	The anhydrous salt loses not more than 2.0%, the monohydrate not more than 15.0%, the dihydrate not more than 25% (60°C, 1 h then 105°C, 4 h)	Anhydrous: Not more than 2% (60°C, 1 h, then 105°C, 4 h) Monohydrate: Not more than 15% (60°C, 1 h, then 105°C, 4 h) Dihydrate: Not more than 25% (60°C, 1 h, then 105°C, 4 h)
Water-insoluble matter	Not more than 0.2% on the anhydrous basis	–
Free acid and disodium phosphate	–	2.00 g of the sample dissolved in 40 mL of water require for neutralisation not more than 0.3 mL of either N sodium hydroxide or N sulfuric acid, using methyl orange TS as indicator
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Cadmium	Not more than 1 mg/kg	
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.3: Specifications established for disodium phosphate (E 339(ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	After drying at 40°C for 3 h and subsequently at 105°C for 5 h, contains not less than 98% of Na_2HPO_4 P_2O_5 content between 49% and 51% on the anhydrous basis	Not less than 98.0% after drying
Description	Anhydrous disodium hydrogen phosphate is a white, hygroscopic, odourless powder. Hydrated forms available include the dihydrate: a white crystalline, odourless solid; the heptahydrate: white, odourless, efflorescent crystals or granular powder; and the dodecahydrate: white, efflorescent, odourless powder or crystals	Anhydrous: White, hygroscopic, odourless powder Dihydrate: White crystalline, odourless solid Heptahydrate: White, odourless, efflorescent crystals or granular powder Dodecahydrate: White, efflorescent, odourless powder or crystals
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water; insoluble in ethanol
pH	Between 8.4 and 9.6 (1% solution)	9.0–9.6 (1 in 100 solution)
Test for orthophosphate	–	Dissolve 0.1 g of the sample in 10 mL water, acidify slightly with dilute acetic acid TS and add 1 mL of silver nitrate TS. A yellow precipitate is formed
Purity		
Loss on drying	The anhydrous salt loses not more than 5.0%, the dihydrate not more than 22.0%, the heptahydrate not more than 50.0%, the dodecahydrate not more than 61.0% (40°C, 3 h then 105°C, 5 h)	Anhydrous: Not more than 5.0% (40°C, 3 h, then 105°C, 5 h). Dihydrate: Not more than 22.0% (40°C, 3 h, then 105°C, 5 h) Heptahydrate: Not more than 50.0% (40°C, 3 h, then 105°C, 5 h) Dodecahydrate: Not more than 61.0% (40°C, 3 h, then 105°C, 5 h)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Water-insoluble matter/substances	Not more than 0.2% on the anhydrous basis	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 50 mg/kg (Method I or III)
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Cadmium	Not more than 1 mg/kg	
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.4: Specifications established for trisodium phosphate (E 339(iii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	Sodium phosphate anhydrous and the hydrated forms, with the exception of the dodecahydrate, contain not less than 97.0% of Na_3PO_4 calculated on the dried basis Sodium phosphate dodecahydrate contains not less than 92.0% of Na_3PO_4 calculated on the ignited basis P_2O_5 content between 40.5% and 43.5% on the anhydrous basis	Anhydrous, hemihydrate and monohydrate: Not less than 97.0% calculated on the dried basis Dodecahydrate: Not less than 92.0% calculated on the ignited basis
Description	White odourless crystals, granules or crystalline powder	White odourless crystals, granules or a crystalline powder; hydrated forms available include hemi- and monohydrates, hexahydrate, octahydrate, decahydrate and dodecahydrate; the dodecahydrate contains 1/4 mol of sodium hydroxide
Identification		
Test for sodium	Passes test	To 5 mL of a 1 in 20 solution of the sample add 1 mL of acetic acid TS and 1 mL of uranyl zinc acetate TS. A yellow crystalline precipitate is formed within a few min
Test for phosphate	Passes test	To 5 mL of a 1 in 100 solution of the sample add 1 mL of concentrated nitric acid and 5 mL of ammonium molybdate TS and warm. A bright canary-yellow precipitate is obtained
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water; insoluble in ethanol
pH	Between 11.5 and 12.5 (1% solution)	11.5–12.5 (1 in 100 solution)
Test for orthophosphate	–	Dissolve 0.1 g of the sample in 10 mL water, acidify slightly with dilute acetic acid TS and add 1 mL of silver nitrate TS. A yellow precipitate is formed
Purity		
Loss on ignition	When dried at 120°C for 2 h and then ignited at about 800°C for 30 min, the losses in weight are as follows: anhydrous not more than 2.0%, monohydrate not more than 11.0%, dodecahydrate: between 45.0% and 58.0%	Anhydrous: Not more than 2% (120°C, 2 h, then 800°C, 30 min) Monohydrate: Not more than 11% (120°C, 2 h, then 800°C, 30 min) Dodecahydrate: 45–58% (120°C, 2 h, then 800°C, 30 min)
Water-insoluble matter/substances	Not more than 0.2% on the anhydrous basis	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 50 mg/kg (Method I or III)
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Cadmium	Not more than 1 mg/kg	
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.5: Specifications established for monopotassium phosphate (E 340(i)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	Content not less than 98.0% after drying at 105°C for 4 h P_2O_5 content between 51.0% and 53.0% on the anhydrous basis	Not less than 98.0% after drying
Description	Odourless, colourless crystals or white granular or crystalline powder	Odourless, colourless crystals or white granular or crystalline powder
Identification		
Test for potassium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water; insoluble in ethanol
pH	Between 4.2 and 4.8 (1% solution)	4.2–4.7 (1 in 100 solution)
Test for orthophosphate	–	To 5 mL of a 1 in 100 solution of the sample, add silver nitrate TS. A yellow precipitate is obtained
Purity		
Loss on drying	Not more than 2.0% (105°C, 4 h)	Not more than 2% (105°C, 4 h)
Water-insoluble matter/substances	Not more than 0.2% on the anhydrous basis	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg See description under TESTS
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.6: Specifications established for dipotassium phosphate (E 340(ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	Content not less than 98% after drying at 105°C for 4 h P_2O_5 content between 40.3% and 41.5% on the anhydrous basis	Not less than 98.0% after drying
Description	Colourless or white granular powder, crystals or masses; deliquescent substance, hygroscopic	Colourless or white granular powder, crystals or masses; deliquescent
Identification		
Test for potassium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water, insoluble in ethanol
pH	Between 8.7 and 9.4 (1% solution)	8.7–9.3 (1 in 100 solution)
Test for orthophosphate		Dissolve 0.1 g of the sample in 10 mL water, acidify slightly with dilute acetic acid TS and add 1 mL of silver nitrate TS. A yellow precipitate is formed

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Purity		
Loss on drying	Not more than 2.0% (105°C, 4 h)	Not more than 5% (105°C, 4 h)
Water-insoluble matter/substances	Not more than 0.2% (on the anhydrous basis)	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg See description under TESTS
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.7: Specifications established for tripotassium phosphate (E 340(iii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation 231/2012	JECFA (2006b,c,d,e,f)
Assay	Content not less than 97% calculated on the ignited basis P_2O_5 content between 30.5% and 34.0% on the ignited basis	Not less than 97.0% of K_3PO_4, calculated on the ignited basis
Description	Colourless or white, odourless hygroscopic crystals or granules. Hydrated forms available include the monohydrate and trihydrate	Colourless or white, odourless hygroscopic crystals or granules; hydrated forms available include the monohydrate and trihydrate
Identification		
Test for potassium	Passes test	To a 1 in 100 solution of the sample add 1 volume of saturated sodium hydrogen tartrate solution and 1 volume of ethanol and shake. A white crystalline precipitate is formed
Test for phosphate	Passes test	To 5 mL of a 1 in 100 solution of the sample add 1 mL of concentrated nitric acid and 5 mL of ammonium molybdate TS and warm. A bright canary-yellow precipitate is obtained
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water; insoluble in ethanol
pH	Between 11.5 and 12.3 (1% solution)	11.5–12.5 (1 in 100 solution)
Test for orthophosphate	–	Dissolve 0.1 g of the sample in 10 mL water, acidify slightly with dilute acetic acid TS and add 1 mL of silver nitrate TS. A yellow precipitate is formed
Purity		
Loss on ignition	Anhydrous: not more than 3.0%; hydrated: not more than 23.0% (determined by drying at 105°C for 1 h and then ignite at about 800 ± 25°C for 30 min)	Anhydrous: Not more than 3% (120°C, 2 h, then 800°C, 30 min) Hydrated: Not more than 23% (120°C, 2 h, then 800°C, 30 min)
Water-insoluble matter/substances	Not more than 0.2% (on the anhydrous basis)	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg See description under TESTS
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.8: Specifications established for calcium dihydrogen phosphate (E 341 (i)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	**JECFA (2006b,c,d,e,f)**
Assay	Content not less than 95% on the dried basis P_2O_5 content between 55.5% and 61.1% on the anhydrous basis	Anhydrous: Not less than 16.8% and not more than 18.3% of Ca Monohydrate: Not less than 15.9% and not more than 17.7% of Ca
Description	Granular powder or white, deliquescent crystals or granules	Hygroscopic white crystals or granules, or granular powder
Identification		
Solubility	–	Sparingly soluble in water, insoluble in ethanol
Test for calcium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
CaO content	Between 23.0% and 27.5% (anhydrous) Between 19.0% and 24.8% (monohydrate)	
Purity		
Loss on drying	Anhydrous: not more than 14% (105°C, 4 h) Monohydrate: not more than 17.5% (105°C, 4 h)	Monohydrate: Not more than 1% (60°C, 3 h)
Loss on ignition	Anhydrous: not more than 17.5% (after ignition at 800 ± 25°C for 30 min) Monohydrate: not more than 25.0% (determined by drying at 105°C for 1 h, then ignite at 800 ± 25°C for 30 min)	Anhydrous: Between 14.0% and 15.5% (800°C, 30 min)
Fluoride	Not more than 30 mg/kg (expressed as fluorine)	Not more than 50 mg/kg Anhydrous: Determine as directed in Method II Monohydrate: Proceed as directed under Method IV
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Cadmium	Not more than 1 mg/kg	
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–
Aluminium	Not more than 70 mg/kg (only if added to food for infants and young children) Not more than 200 mg/kg (for all uses except food for infants and young children)	–

Table E.9: Specifications established for calcium hydrogen phosphate (E 341(ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	**JECFA (2006b,c,d,e,f)**
Assay	Dicalcium phosphate, after drying at 200°C for 3 h, contains not less than 98% and not more than the equivalent of 102% of $CaHPO_4$ P_2O_5 content between 50.0% and 52.5% on the anhydrous basis	Not less than 98.0% and not more than the equivalent of 102.0% after drying
Description	White crystals or granules, granular powder or powder	White crystals or granules, granular powder or powder
Identification		
Solubility	Sparingly soluble in water. Insoluble in ethanol	Sparingly soluble in water; insoluble in ethanol
Test for calcium	Passes test	Passes test

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Test for phosphate	Passes test	Passes test
Purity		
Loss on drying	–	Anhydrous: Not more than 2% (200°C, 3 h) Dihydrate: Not less than 18% and not more than 22% (200°C, 3 h)
Loss on ignition	Not more than 8.5% (anhydrous), or 26.5% (dihydrate) after ignition at 800 ± 25°C for 30 min	–
Fluoride	Not more than 50 mg/kg (expressed as fluorine)	Not more than 50 mg/kg (Method I or III)
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg (Method II)
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Cadmium	Not more than 1 mg/kg	–
Mercury	Not more than 1 mg/kg	–
Aluminium	Not more than 100 mg/kg for the anhydrous form and not more than 80 mg/kg for the dihydrated form (only if added to food for infants and young children) Not more than 600 mg/kg for the anhydrous form and not more than 500 mg/kg for the dihydrated form (for all uses except food for infants and young children). This applies until 31 March 2015 Not more than 200 mg/kg for the anhydrous form and the dihydrated form (for all uses except food for infants and young children). This applies from 1 April 2015	–

Table E.10: Specifications established for tricalcium phosphate (E 341(iii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	Content not less than 90% calculated on the ignited basis P_2O_5 content between 38.5% and 48.0% on the anhydrous basis	Not less than the equivalent of 90% of $Ca_3(PO_4)_2$, calculated on the ignited basis
Description	A white, odourless powder which is stable in air	White, odourless powder which is stable in air
Identification		
Solubility	Practically insoluble in water; insoluble in ethanol, soluble in dilute hydrochloric and nitric acid	Practically insoluble in water; insoluble in ethanol, soluble in dilute hydrochloric and nitric acid
Test for calcium	Passes test	Dissolve about 100 mg of the sample by warming with 5 mL of dilute hydrochloric acid TS and 5 mL of water. Add 1 mL of ammonia TS, dropwise, with shaking and then add 5 mL of ammonium oxalate TS. A white precipitate forms
Test for phosphate	Passes test	To a warm solution of the sample in a slight excess of nitric acid add ammonium molybdate TS. A yellow precipitate forms

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Purity		
Loss on ignition	Not more than 8% after ignition at 800 ± 25°C for 0.5 h	Not more than 10% after ignition at 825°C to constant weight
Fluoride	Not more than 50 mg/kg (expressed as fluorine)	Not more than 50 mg/kg (Method I or III)
Arsenic	Not more than 1 mg/kg	
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Cadmium	Not more than 1 mg/kg	–
Mercury	Not more than 1 mg/kg	–
Aluminium	Not more than 150 mg/kg (only if added to food for infants and young children) Not more than 500 mg/kg (for all uses except food for infants and young children). This applies until 31 March 2015 Not more than 200 mg/kg (for all uses except food for infants and young children). This applies from 1 April 2015	–

Table E.11: Specifications established for monomagnesium phosphate (E 343(i)) according to Commission Regulation (EU) No 231/2012 and JECFA (2008)

	Commission Regulation No 231/2012	JECFA (2008)
Assay	Not less than 51.0% after ignition calculated as P_2O_5 at the ignited basis (800 ± 25°C for 30 min)	Not less than 96% and not more than 102% as $Mg_2P_2O_7$ on the ignited basis
Description	White, odourless, crystalline powder	White, odourless, crystalline powder
Identification		
Solubility	Slightly soluble in water	Slightly soluble in water
Test for magnesium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Purity		
Loss on drying		Anhydrous: Not more than 1.5% (105°C, 4 h)
Loss on ignition		Anhydrous: Not more than 18.5% Dihydrate: Not more than 33% Tetrahydrate: Not more than 43%
MgO content	Not less than 21.5% after ignition or at an anhydrous basis (105°C, 4 h)	–
Fluoride	Not more than 10 mg/kg (as fluorine)	Not more than 10 mg/kg See description under TESTS
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Cadmium	Not more than 1 mg/kg	–
Mercury	Not more than 1 mg/kg	–

Table E.12: Specifications established for dimagnesium phosphate (E 343(ii)) according to Commission Regulation (EU) No 231/2012 and JECFA (2006a)

	Commission Regulation No 231/2012	JECFA (2006b,c,d,e,f)
Assay	Not less than 96% after ignition (800 ± 25°C for 30 min)	Not less than 96.0% on the ignited basis
Description	White, odourless, crystalline powder	Odourless white crystalline powder
Identification		
Solubility	Slightly soluble in water	Slightly soluble in water, soluble in dilute acids, but insoluble in ethanol
Test for magnesium	Passes test	Dissolve 100 mg in 0.5 mL of diluted acetic acid TS and 20 mL of water. Add 1 mL of ferric chloride TS, let stand for 5 min and filter. The filtrate gives a positive test for magnesium
Test for phosphate	Passes test	Passes test
Purity		
Loss on ignition		Not less than 29% and not more than 36% (800 ± 25°C to constant weight)
MgO content	Not less than 21.5% after ignition or at an anhydrous basis (105°C, 4 h)	–
Fluoride	Not more than 10 mg/kg (as fluorine)	Not more than 10 mg/kg (Method III)
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Cadmium	Not more than 1 mg/kg	–
Mercury	Not more than 1 mg/kg	–

Table E.13: Specifications for disodium diphosphate (E 450(i)) according to Commission Regulation (EU) No 231/2012 and as INS 450(i) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 95% of disodium diphosphate. P_2O_5 content not less than 63.0% and not more than 64.5%	Not less than 95.0%
Description	White powder or grains	White, crystalline powder or granules
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Soluble in water	Soluble in water
pH	Between 3.7 and 5.0 (1% solution)	3.7–5.0 (1 in 100 solution)
Purity		
Loss on drying	Not more than 0.5% (105°C, 4 h)	Not more than 0.5% (105°, 4 h)
Water-insoluble matter	Not more than 1%	Not more than 1%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–
Aluminium	No more than 200 mg/kg	–

Table E.14: Specifications for trisodium diphosphate (E 450(ii)) according to Commission Regulation (EU) No 231/2012 and as INS 450(ii) according to JECFA (2012a,b).

	Commission Regulation (EU) No 231/2012	**JECFA (2012a,b)**
Assay	Content not less than 95% on the dried basis. P_2O_5 content not less than 57% and not more than 59%	Not less than 57% and not more than 59% expressed as P_2O_5 on the dried basis
Description	White powder or grains, occurs anhydrous or as a monohydrate	White powder or grains
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Soluble in water	Soluble in water
pH	Between 6.7 and 7.5 (1% solution)	–
Purity		
Loss on ignition	Not more than 4.5% on the anhydrous compound (450–550°C). Not more than 11.5% on the monohydrate basis	Anhydrous: not more than 4.5 Monohydrate: not more than 11.5%
Loss on drying	Not more than 0.5% (105°C, 4 h) for anhydrous Not more than 1.0% (105°C, 4 h) for monohydrate	Anhydrous: not more than 0.5% (105°, 4 h) Monohydrate: not more than 1.0% (105°, 4 h)
Water-insoluble matter	Not more than 0.2%	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.15: Specifications for tetrasodium diphosphate (E 450(iii)) according to Commission Regulation (EU) No 231/2012 and as INS 450(iii) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	**JECFA (2012a,b)**
Assay	Content not less than 95% of $Na_4P_2O_7$ on the ignited basis. P_2O_5 content not less than 52.5% and not more than 54.0%	Not less than 95.0% on the ignited basis
Description	Colourless or white crystals, or a white crystalline or granular powder. The decahydrate effloresces slightly in dry air	Colourless or white crystals, or a white crystalline or granular powder; the decahydrate effloresces slightly in dry air
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Soluble in water. Insoluble in ethanol	Soluble in water. Insoluble in ethanol
pH	Between 9.8 and 10.8 (1% solution)	9.9–10.8 (1 in 100 solution)
Purity		
Loss on ignition	Not more than 0.5% for the anhydrous salt, not less than 38% and not more than 42% for the decahydrate (105°C, 4 h then 550°C, 30 min	Not more than 0.5% for anhydrous, 38–42% for decahydrate (105°, 4 h then 550°, 30 min)
Water-insoluble matter	Not more than 0.2%	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.16: Specifications for tetrapotassium diphosphate (E 450(v)) according to Commission Regulation (EU) No 231/2012 and as INS 450(v) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 95% (800°C for 0.5 h). P_2O_5 content not less than 42.0% and not more than 43.7%	Not less than 95% on the ignited basis
Description	Colourless crystals or white, very hygroscopic powder	Colourless or white crystals, or a white crystalline or granular powder, powder of granular solid; hygroscopic
Identification		
Test for potassium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Soluble in water Insoluble in ethanol	Soluble in water Insoluble in ethanol
pH	Between 10.0 and 10.8 (1% solution)	10.0–10.7 (1 in 100 solution)
Purity		
Loss on ignition	Not more than 2% (105°C, 4 h then 550°C, 30 min	Not more than 2% (105°, 4 h; then 550°, 30 min)
Water-insoluble matter	Not more than 0.2%	Not more than 0.2%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.17: Specifications for dicalcium diphosphate (E 450(vi)) according to Commission Regulation (EU) No 231/2012 and as INS 450(vi) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 96%. P_2O_5 content not less than 55% and not more than 56%	Not less than 96%
Description	A fine, white, odourless powder	Fine, white, odourless powder
Identification		
Test for calcium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Insoluble in water Soluble in dilute hydrochloric and nitric acids	Insoluble in water Soluble in dilute hydrochloric and nitric acids
pH	Between 5.5 and 7.0 (10% suspension in water)	5.5–7.0 (1 in 10 slurry)
Purity		
Loss on ignition	Not more than 1.5% (800 ± 25 °C, 30 min)	Not more than 1.5%
Fluoride	Not more than 50 mg/kg (expressed as fluorine)	Not more than 50 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.18: Specifications for calcium dihydrogen diphosphate (E 450(vii)) according to Commission Regulation (EU) No 231/2012 and as INS 450(vii) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 90% on the anhydrous basis. P_2O_5 content not less than 61% and not more than 66%	Not more than 64% expressed as P_2O_5 on dried basis
Description	White crystals or powder	White crystals or powder
Identification		
Test for calcium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Purity		
Loss on drying	–	Anhydrous: not more than 1% (105°, 4 h)
Acid-insoluble matter	Not more than 0.4%	Not more than 0.4%
Fluoride	Not more than 30 mg/kg (expressed as fluorine)	Not more than 30 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–
Aluminium	Not more than 800 mg/kg This applies until 31 March 2015 Not more than 200 mg/kg This applies from 1 April 2015	–

Table E.19: Specifications for magnesium dihydrogen diphosphate (E 450(ix)) according to Commission Regulation (EU) No 231/2012 and as INS 450(ix) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	P_2O_5 content not less than 68.0% and not more than 70.5% expressed as P_2O_5MgO content not less than 18.0% and not more than 20.5% expressed as MgO	
Description	White crystals or powder	
Identification		
Solubility	Slightly soluble in water, practically insoluble in ethanol	
Particle size	The average particle size will deviate between 10 and 50 μm	
Test for magnesium		Passes test
Purity		
Loss on ignition	Not more than 12% (800°C, 0.5 h)	Not more than 12% (800°C, 0.5 h)
Orthophosphate		Not more than 4% as $(PO_4)^{3-}$
Calcium		Not more than 4%
Fluoride	Not more than 20 mg/kg (expressed as fluorine)	Not more than 20 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 1 mg/kg

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Cadmium	Not more than 1 mg/kg	Not more than 1 mg/kg
Lead	Not more than 1 mg/kg	Not more than 1 mg/kg
Aluminium	Not more than 50 mg/kg	Not more than 50 mg/kg

Table E.20: Specifications for pentasodium triphosphate (E 451(i)) according to Commission Regulation (EU) No 231/2012 and as INS 451(i) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 85.0% (anhydrous) or 65.0% (hexahydrate) P_2O_5 content not less than 56% and not more than 59% (anhydrous) or not less than 43% and not more than 45% (hexahydrate)	Anhydrous: not less than 85.0% of $Na_5O_{10}P_3$ and not less than 56.0% and not more than 58.0% of P_2O_5 Hexahydrate: not less than 65.0% of $Na_5O_{10}P_3$ and not less than 43.0% and not more than 45.0% of P_2O_5
Description	White, slightly hygroscopic granules or powder	White, slightly hygroscopic granules or powder
Identification		
Test for sodium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Freely soluble in water. Insoluble in ethanol	Freely soluble in water. Insoluble in ethanol
pH	Between 9.1 and 10.2 (1% solution)	Between 9.1 and 10.1 (1% solution)
Purity		
Loss on drying	Anhydrous: not more than 0.7% (105°C, 1 h) Hexahydrate: not more than 23.5% (60°C, 1 h, then 105°C, 4 h)	Anhydrous: not more than 0.7% (105°, 1 h) Hexahydrate: not more than 23.5% (60°, 1 h, followed by 105°, 4 h)
Water-insoluble matter	Not more than 0.1%	Not more than 0.1%
Higher polyphosphates	Not more than 1%	Not detectable
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 50 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.21: Table 2 Specifications for pentapotassium triphosphate (E 451(ii)) according to Commission Regulation (EU) No 231/2012 and as INS 451(i) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	Content not less than 85% on the anhydrous basis	Not less than 85% of $K_5O_{10}P_3$ on the dried basis, the remainder being principally other potassium phosphates
Description	White, very hygroscopic powder or granules	Hygroscopic white granules or powder
Identification		
Test for potassium	Passes test	Passes test
Test for phosphate	Passes test	Passes test
Solubility	Very soluble in water	Very soluble in water
pH	Between 9.2 and 10.5 (1% solution)	Between 9.2 and 10.1 (1% solution)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Purity		
Loss on ignition	Not more than 0.4% (105°C, 4 h, then 550°C, 30 min)	Not more than 0.4% after drying (105°, 4 h) followed by ignition at 550° for 30 min)
Water-insoluble matter	Not more than 2%	Not more than 2%
P_2O_5 content	P_2O_5 content not less than 46.5% and not more than 48%	Not less than 46.5% and not more than 48.0%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.22: Specifications for sodium polyphosphate (E 452(i) I. Soluble polyphosphate) according to Commission Regulation (EU) No 231/2012 and as INS 452(i) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	JECFA (2012a,b)
Assay	P_2O_5 content not less than 60% and not more than 71% on the ignited basis	Not less than 60.0% and not more than 71.0% of P_2O_5
Description	Colourless or white, transparent platelets, granules or powders	Colourless or white, transparent platelets, granules or powders
Identification		
Test for sodium	Passes test	A 1 in 20 solution passes test
Test for phosphate	Passes test	Dissolve 0.1 g of the sample in 5 mL of hot dilute nitric acid TS. Warm on a steam bath for 10 min and cool. Neutralise to litmus with sodium hydroxide TS, and add silver nitrate TS. A yellow precipitate is formed which is soluble in dilute nitric acid TS
Solubility	Very soluble in water	Very soluble in water
pH	Between 3.0 and 9.0 (1% solution)	–
Purity		
Loss on ignition	Not more than 1%	Not more than 1.0%
Water-insoluble matter	Not more than 0.1%	Not more than 0.1%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.23: Specifications for sodium polyphosphate (E 452(i) II. insoluble polyphosphate) according to Commission Regulation (EU) No 231/2012 and as INS 452(i) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012
Assay	P_2O_5 content not less than 68.7% and not more than 70.0%
Description	White crystalline powder
Identification	
Test for sodium	Passes test
Test for phosphate	Passes test
Solubility	Insoluble in water, soluble in mineral acids and in solutions of potassium and ammonium (but not sodium) chlorides
pH	About 6.5 (1 in 3 suspension in water)
Purity	
Fluoride	Not more than 10 mg/kg (expressed as fluorine)
Arsenic	Not more than 1 mg/kg
Cadmium	Not more than 1 mg/kg
Lead	Not more than 1 mg/kg
Mercury	Not more than 1 mg/kg

Table E.24: Specifications for potassium polyphosphate (E 452(ii)) according to Commission Regulation (EU) No 231/2012 and as INS 452(ii) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	**JECFA (2012a,b)**
Assay	P_2O_5 content not less than 53.5% and not more than 61.5% on the ignited basis	Not less than 53.5% and not more than 61.5% of P_2O_5 on the ignited basis
Description	Fine white powder or crystals or colourless glassy platelets	Odourless, colourless or white glassy masses, fragments, crystals or powder
Identification		
Test for potassium	Passes test	Mix 0.5 g of the sample with 10 mL of nitric acid and 50 mL of water, boil for about 30 min and cool. The resulting solution is used for the test
Test for phosphate	Passes test	Mix 0.5 g of the sample with 10 mL of nitric acid and 50 mL of water, boil for about 30 min and cool. The resulting solution is used for the test
Solubility	1 g dissolves in 100 mL of a 1 in 25 solution of sodium acetate	1 g dissolves in 100 mL of a 1 in 25 solution of sodium acetate
pH	Not more than 7.8 (1% suspension)	–
Purity		
Loss on ignition	Not more than 2% (105°C, 4 h then 550°C, 30 min)	Not more than 2% after drying (105°, 4 h) followed by ignition at 550°C for 30 min
Cyclic phosphate	Not more than 8% on P_2O_5 content	Not more than 8.0%
Fluoride	Not more than 10 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.25: Specifications for sodium calcium polyphosphate (E 452(iii)) according to Commission Regulation (EU) No 231/2012 and as INS 452(iii) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	**JECFA (2012a,b)**
Assay	P_2O_5 content not less than 61% and not more than 69% on the ignited basis	Not less than 61% and not more than 69% expressed as P_2O_5 on dried basis
Description	White glassy crystals, spheres	White glassy crystals, spheres
Identification		
Test for sodium	–	Passes test
Test for calcium	–	Passes test
Test for phosphate	–	Passes test
pH	Approximately 5–7 (1% m/m slurry)	–
CaO content	7–15% m/m	–
Purity		
Fluoride	Not more than 10 mg/kg	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Table E.26: Specifications for calcium polyphosphate (E 452(iv)) according to Commission Regulation (EU) No 231/2012 and as INS 452(iv) according to JECFA (2012a,b)

	Commission Regulation (EU) No 231/2012	**JECFA (2012a,b)**
Assay	P_2O_5 content not less than 71% and not more than 73% on the ignited basis	Not less than 50.0 and not more than 71.0% of P_2O_5 on the ignited basis
Description	Odourless, colourless crystals or white powder	Odourless, colourless crystals or powder
Identification		
Test for calcium	Passes test	The solution of the test for phosphate gives positive tests for calcium
Test for phosphate	Passes test	Mix 0.5 g of the sample with 10 mL of nitric acid and 50 mL of water, boil for about 30 min and cool. The resulting solution is used for the test
Solubility	Usually sparingly soluble in water. Soluble in acid medium	Usually incompletely soluble in water; soluble in acid medium
CaO content	27–29.5%	–
Purity		
Loss on ignition	Not more than 2% (105°C, 4 h than 550°C, 30 min)	Not more than 2% after drying (105°C, 4 h) followed by ignition (550°C, 30 min)
Cyclic phosphate	Not more than 8% (on P_2O_5 content)	Not more than 8% calculated on P_2O_5 content
Fluoride	Not more than 30 mg/kg (expressed as fluorine)	Not more than 10 mg/kg
Arsenic	Not more than 1 mg/kg	Not more than 3 mg/kg
Cadmium	Not more than 1 mg/kg	–
Lead	Not more than 1 mg/kg	Not more than 4 mg/kg
Mercury	Not more than 1 mg/kg	–

Appendix F – Summary of the reported use levels (mg/kg or mg/L as appropriate) of phosphates (E 338–341, E 343, E 450–452) provided by industry

Appendix G – Summary of analytical results (mg P/kg or mg P/L as appropriate) of phosphorus provided by Member States

Appendix H – Number and percentage of food products labelled with phosphates (E 338-341, E 343, E 450-452) out of the total number of food products present in the Mintel GNPD per food subcategory between 2014 and 2019

Appendix I – Concentration levels of phosphates (E 338–341, E 343, E 450–452) used in the regulatory maximum level exposure assessment scenario and in the refined exposure assessment scenarios (mg/kg or mL/kg as appropriate)

Appendix J – Summary of total estimated exposure of phosphates (E 338–341, E 343, E 450–452) from their use as food additives for the regulatory maximum level exposure assessment scenario and the refined exposure assessment scenarios, in seven population groups (min-max across the dietary surveys in mg P_2O_5/kg bw per day and in mg P_2O_5/ person per day)

Appendix K – Total estimated exposure of phosphates (E 338–341, E 343, E 450–452) from their use as food additives for the regulatory maximum level exposure assessment scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg P_2O_5/kg bw per day)

Appendix L – Main food categories contributing to exposure to phosphates (E 338–341, E 343, E 450–452) using the regulatory maximum level exposure assessment scenario and the refined exposure assessment scenarios, based on the results expressed in mg P_2O_5/kg bw per day (> 5% to the total mean exposure)

Appendix M

M1: Summary of total estimated exposure of phosphates (E 338–341, E 343, E 450–452) from their use as food additives and the proposed extension of uses for the regulatory maximum level exposure assessment scenario and the refined exposure assessment scenarios (min–max across the dietary surveys in mg P_2O_5/kg bw per day and in mg P_2O_5/person per day)

M2: Total estimated exposure of phosphates (E 338–341, E 343, E 450–452) from their use as food additives and the proposed extension of use for the regulatory maximum level exposure assessment scenario and the refined exposure assessment scenarios per population group and survey: mean and 95th percentile (mg P_2O_5/kg bw per day)

Appendix N

N1: Summary of exposure to total phosphorus via the diet (using analytical data) per population group and survey: mean and 95th percentile (mg P/kg bw per day)

N2: Summary of exposure to total phosphorus via the diet (using analytical data) per population group and survey: mean and 95th percentile (mg P/person per day)

Appendix O – Main food categories contributing to exposure to total phosphorus via the diet (using analytical data, based on exposure in mg P/kg bw per day) (> 5% to the total mean exposure)

Appendices F–O can be found in the online version of this output ('Supporting information' section): https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2019.5674

Appendix P – Case series and case reports after acute administration

Case series and case reports after acute administration							
No.	**Author**	**Age/ sex**	**History**	**Dose given in mg of phosphorus Oral Solution**	**Outcome**	**Serum creatinine levels (mg/dL)**	**Clinical/ pathological observation**
1	Aasebø et al. (2007)	69/F	Breast cancer. Hypertension	11,600 (2 × 5,800 within 12 h)	Remission	Baseline: 0.79 Onset: 4.32–5.97 Follow-up: 1.60	Baseline: diagnosis of membranous glomerulonephritis (?) after the increase of creatinine > 5.97, in a second biopsy calcium phosphate deposits
2	Arikan et al. (2013)	18/F	Ileus	11,600 (2 × 5,800 within 12 h)	Haemodialysis remission	Baseline: 0.41 Onset: 0.87–1.08 Follow-up: 0.60	
3	Cakar et al. (2012)	65/M	Hypertension	11,600 (2 × 5,800 within 12 h)	CKD. Patient started haemodialysis treatment	Baseline: 1.14 Onset: 1.82 Follow-up: 3.14	Kidney biopsy showed mild focal tubulointerstitial inflammation, tubular atrophy, sclerosis
4	Fine and Patterson (1997)	84/F	Hypertension, mild cardiac insufficiency.	34,800 (6 × 5,800) over 4 days	Death	Baseline: 0.7 Onset: 2.5 –	
5	Gonlusen et al. (2006)	56/F	Gastroesophageal reflux, mild Crohn's disease	11,600 (2 × 5,800 within 12 h)	Remission	Baseline: 0.8 Onset: 3.8 Follow-up: 1.6	Renal biopsy (44 days after colonoscopy) nephrocalcinosis
6	Markowitz et al. (2004)	69/M	HTA (losartan), carcinoma, mild hyperparathyroidism. Folic acid	11,600 (2 × 5,800 within 12 h)	Unknown	Baseline: 1.2 Onset: 6.7–8.5 Follow-up: –	After the colonoscopy, the patient presented with an episode of gross haematuria
7	Markowitz et al. (2004)	82/M	Hypertension. Surgical intervention with hemicolectomy	15,500 (2 × 5,800 = 11,600 within 12 h) + 3,900	Unknown	Baseline: 0.9 Onset: 5.2–4.9 Follow-up: 4.3	
8	Markowitz et al. (2004)	55/F	Diabetes mellitus, Hypertension, coronary heart disease	11,600 (2 × 5,800 within 12 h)	Unknown	Baseline: 0.6 Onset: 4.5 Follow-up: 3.5	
9	Markowitz et al. (2004)	64/F	hypertonia arterialis (enalapril, HCT, aspirin) diabetes mellitus (glipizide, rosiglitazone), obesity. Use of KCL. Adenomatous rectal polyp	11,600 (2 × 5,800 within 12 h)	Unknown	Baseline: 0.9 Onset: 2.3 Follow-up: 3.3	

Case series and case reports after acute administration							
No.	**Author**	**Age/ sex**	**History**	**Dose given in mg of phosphorus Oral Solution**	**Outcome**	**Serum creatinine levels (mg/dL)**	**Clinical/ pathological observation**
10	Markowitz et al. (2004)	76/F	Hypertension),	11,600 (2 × 5,800 within 12 h)	Unknown	Baseline: 0.9 Onset: 6.0–8.0 Follow-up: 3.7	Patient needed haemodialysis
11	Orias et al. (1999)	76/M	Hypertension	29,000 (5 × 5,800 within 2 days)	Remission, without further haemodialysis	Baseline: 1.1 Onset: 2.5–3.7 Follow-up: 1.3	Haemodialysis was initiated
12	Santos et al. (2010)	84/M	History of stage 3 obstructive CRF	11,600 (2 × 5,800 10–12 h apart)	Regular haemodialysis	Baseline: – Onset: 9.2 Follow-up: –	Kidney biopsy showed tubules were mildly dilated and nephrocalcinosis
13	Santos et al. (2010)	88/M	B-cell lymphoma IV-B stage	11,600 (2 × 5,800 10–12 h apart)	Phosphate nephropathy. No clinical improvement Death	Baseline: – Onset: 3.45 –	Renal ultrasound showed kidneys with enhanced echogenicity
14	Slee et al. (2008)	62/F	Hypertension	11,600 (2 × 5,800 within 12 h)	CKD stage 4	Baseline: 0.83 Onset: 1.97–4.95 Follow-up: 1.8	Kidney biopsy (on day 10) nephrocalcinosis with diffuse non-polarising tubular deposits in the tubulointerstitium
15	Vukasin et al. (1997)	69/F	Unknown	23,200 (2 × 5,800 12 h apart) + 5,800 × 2 (5 h apart)	Remission	Baseline: – Onset: 1.7–2.3 Follow-up: Normal	

CKD: chronic kidney disease.; HTA: Hypertonia arterialis; HCT: hychlorothiazide; KCl: Potassium chloride; CRF: corticotropin-releasing factor.

Appendix Q – Interventional studies – short-term exposure

	Interventional studies – short–term exposure						
	Authors (publication year)	**Title**	**Number of patients**	**Phosphorus dose (mg/day)**	**Duration of exposure (days)**	**Renal function**	**Bowel complaints**
1	Brixen et al. (1992)	Effects of a Short Course of Oral Phosphate Treatment on Serum Parathyroid Hormone (I-84) and Biochemical Markers of Bone Turnover: A Dose-Response Study	19 19 20	750 1,500 2,250	7 7 7	No change in serum creatinine mentioned	2 patients 3 patients 7 patients
2	Ittner et al. (1986)	Reduced parathyroid hormone response to peroral phosphate in osteoporotic patients	7	1,500	1	No change in serum creatinine	Not mentioned
3	Portale et al. (1987)	Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for renal production of 1,25-dihydroxyvitamin D	6	1,000 2,500	9 10	No change in serum creatinine	Not mentioned
4	Silverberg et al. (1986)	The effect of oral phosphate administration on major indices of skeletal metabolism in normal subjects	13	660	5	Not mentioned	Not mentioned
5	Smith and Nordin (1964)	The effect of a high phosphorus intake on total and ultrafiltrable plasma calcium and phosphate clearance.	8	1,500	7–10	Not mentioned	Not mentioned
6	Van Den Berg et al. (1980)	Orthophosphate therapy decreases urinary calcium excretion and 1,25 $(OH)_2D$ concentration in idiopathic hypercalciuria	11	2,000	14	Not mentioned	Not mentioned
7	Yamaoka et al. (1989)	Effect of single oral phosphate loading on vitamin D metabolites in normal subjects and in X-linked hypophosphatemic rickets	7	2,000	1	No change in serum creatinine	Not mentioned

Appendix R – Interventional studies – long-term exposure

	Interventional studies – long-term exposure						
	Authors (publication year)	**Title**	**Number of patients**	**Phosphorus dose (mg/day)**	**Duration of exposure (months)**	**Renal function**	**Bowel complaints**
1	Alexandre et al. (1988)	Effects of a one-year administration of phosphate and intermittent calcitonin on bone-forming and bone-resorbing cells in involutional osteoporosis: a histomorphometric study	15	500	12	Not mentioned as reduced	Not mentioned
2	Bernstein and Newton (1966)	The effect of oral sodium phosphate on the formation of renal calculi and on idiopathic hypercalcuria	10	2,400 (4 patients) 4,800 (5 patients) 7,200 (1 patient)	6–24 4–24 24	Slightly reduced (1 patient) reduced (2 patients) 50% reduction	Not mentioned
3	Calvo et al. (1990)	Persistently Elevated Parathyroid Hormone Secretion and Action in Young Women after Four Weeks of Ingesting High Phosphorus, Low Calcium Diets.	10	807 (1,723 (phosphate-rich diet)–916 (basal diet))	1	Not mentioned	Not mentioned
4	Dudley and Blackburn (1970)	Extraskeletal calcification complicating oral neutral phosphate therapy	9	2,250 (1) 3,375 (7) 4,500 (1)	9–87	Renal function decreased (2 patients: 3,375 and 4,500)	Not mentioned
5	Ettinger (1976)	Recurrent Nephrolithiasis: Natural History and Effect of Phosphate Therapy.	25	1,400	36	No changes in renal function, or creatinine mentioned	Stool softness
6	Goldsmith et al. (1968)	Phosphate supplementation as an adjunct in the therapy of multiple myeloma.	10	Nine patients 1,000 one patient 2,000	0.75–9	No deterioration of renal function	Not mentioned
7	Goldsmith et al. (1976)	Hormone and bone morphology in osteoporosis effects of phosphorus supplementation on serum parathyroid	7	1,000	3–20	Inulin clearance and PAH clearance not changed	Not mentioned

	Interventional studies – long-term exposure						
	Authors (publication year)	**Title**	**Number of patients**	**Phosphorus dose (mg/day)**	**Duration of exposure (months)**	**Renal function**	**Bowel complaints**
8	Hulley et al. (1971)	The effect of supplemental oral phosphate on the bone mineral changes during prolonged bed rest	5	1,327	4	No changes of creatinine clearance	Not mentioned
9	Kuntz et al. (1986)	Treatment of post-menopausal osteoporosis with phosphate and intermittent calcitonin	10	535 (1,500 mg/ day for 5 days every third week for 6 months)	6	No changes in renal function, or creatinine mentioned	Not mentioned
10	Miller et al. (1991)	Effect of cyclical therapy with phosphorus and etidronate on axial bone mineral density in postmenopausal osteoporotic women	47	65.75 (for 3 days a dose of 2,000 mg, 8 times over 2 years)	24	No changes in renal function, or creatinine mentioned	Not mentioned
12	Popovtzer et al. (1976)	Effects of alternating phosphorus and calcium infusions on osteoporosis	5	150–300 (5–10 mg/kg bw per day: 3 days per week)	10–12	No change in creatinine clearance (pre vs. post)	Not mentioned
13	Bell et al. (1977)	Physiological responses of human adults to foods containing phosphate additives	8	1,100	1	Not mentioned	Not mentioned
14	Shapiro et al. (1975)	Osteoporosis	10	2,200	12–24	No changes in serum creatinine mentioned	Not mentioned
15	Ulmann et al. (1984)	Fréquence des récifdives lithiasiques après une curre de diurèse simple ou assiciée à un traitement par un duirétique thiazidique ou le phophore	13	1,500	24 (median)	No change in serum creatinine mentioned	Not mentioned
16	Whybro et al. (1998)	Phosphate supplementation in young men: lack of effect on calcium homeostasis and bone turnover	12	1,000, 1,500 and 2,000 (escalating)	3	No change in serum creatinine	Not mentioned

Appendix S – Phosphorus intake, middle and high intakes (mg/day), reported in human studies referenced in the present opinion

Author (year)	Middle phosphate intake (mg/day)	Highest expressed phosphate intake (mg/day)	Country	Dietary assessment method
Alonso et al. (2010)	1,084 (ARIC-study) mean	2,856 (highest)	USA	FFQ (66 items)
	1,103 (MESA-study)	3,570 (highest)	USA	FFQ (120 items)
Yamamoto et al. (2013)	1,167 (men) 1,017 (women)	5,032 (men) 4,069 (women) maximum intake	USA	FFQ (120 items)
Kwak et al. (2014)	759 median	976 75th percentile	Korea	FFQ (103 items)
Mazidi et al. (2017)	1,222 median	1,641 highest 75th percentile	Iran	Single 24-h recall
Chang et al. (2014)	1,166 median	2,355 (75th percentile in highest quartile)	USA	Single 24-h recall
Itkonen et al. (2013)	1,617	1,795 ± 469 (SD) males	Finland	3 day food record + FFQ
Tucker et al. (2006)	1,198–1,206 (categorised by cola consumption) adjusted for age and energy intake	1,206 ± 10 mean ± SD adjusted for age and energy intake	USA	FFQ (126 items)

FFQ: food frequency questionnaires.

Annex 1 – Newcastle–Ottawa quality assessment scale case control studies

NEWCASTLE – OTTAWA QUALITY ASSESSMENT SCALE
CASE–CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✵
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✵
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✵
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✵
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview where blind to case/control status ✵
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✵
   b) no

3) Non-Response rate
   a) same rate for both groups ✵
   b) non respondents described
   c) rate different and no designation

NEWCASTLE – OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✵
   b) somewhat representative of the average _____ in the community ✵
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✵
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✵
   b) structured interview ✵
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✵
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✵
   b) study controls for any additional factor ✵ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✵
   b) record linkage ✵
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✵
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✵
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✵
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Annex 2 – Coding manual for case control and cohort studies

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1) Is the Case Definition Adequate?

a) Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) ☆
b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record
c) No description

2) Representativeness of the Cases

a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample) ☆
b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (i.e. same community as cases and would be cases if had outcome) ☆
b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
c) No description

4) Definition of Controls

a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. ☆
b) No mention of history of outcome

COMPARABILITY

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age =☆ , Other controlled factors = ☆

EXPOSURE

1) Ascertainment of Exposure

Allocation of stars as per rating sheet

2) Non-Response Rate

Allocation of stars as per rating sheet

CODING MANUAL FOR COHORT STUDIES

SELECTION

1) Representativeness of the Exposed Cohort

Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health oriented women are likely to be representative of postmenopausal estrogen users while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of estrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users users of estrogen).

Allocation of stars as per rating sheet

2) Selection of the Non-Exposed Cohort

Allocation of stars as per rating sheet

3) Ascertainment of Exposure

Allocation of stars as per rating sheet

4) Demonstration That Outcome of Interest Was Not Present at Start of Study

In the case of mortality studies, outcome of interest is still the presence of a disease/ incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

COMPARABILITY

1) Comparability of Cohorts on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category
Either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)
Age = ☆ , Other controlled factors = ☆

OUTCOME

1) Assessment of Outcome

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.) ☆
b) Record linkage (e.g. identified through ICD codes on database records) ☆
c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)
d) No description.

2) Was Follow-Up Long Enough for Outcomes to Occur

An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants)

3) Adequacy of Follow Up of Cohorts

This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.

Allocation of stars as per rating sheet

Annex 3 – STROBE Statement—Checklist of items that should be included in reports of cross-sectional studies

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Sodium and phosphorus-based food additives: persistent but surmountable hurdles in the management of nutrition in chronic kidney disease

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Abstract

Sodium and phosphorus-based food additives are among the most commonly consumed nutrients in the world. This is because both have diverse applications in processed food manufacturing, leading to their widespread utilization by the food industry. Since most foods are naturally low in salt, sodium additives almost completely account for the excessive consumption of sodium throughout the world. Similarly, phosphorus additives represent a major and “hidden” phosphorus load in modern diets. These factors pose a major barrier to successfully lowering sodium or phosphorus intake in patients with chronic kidney disease. As such, any serious effort to reduce sodium or phosphorus consumption will require reductions in the use of these additives by the food industry. The current regulatory environment governing the use of food additives does not favor this goal, however, in large part because these additives have historically been classified as generally safe for public consumption. To overcome these barriers, coordinated efforts will be needed to demonstrate that high intakes of these additives are not safe for public consumption and as such, should be subject to greater regulatory scrutiny.

Keywords: nutrition, diet, sodium, phosphorus, chronic kidney disease

INTRODUCTION

Sodium-based food additives are among the most abundantly consumed nutrients in the world. This is because sodium salts are not only effective anti-spoilage agents, they can also serve as relatively cheap taste enhancers in a variety of foods. As a result, sodium additives are heavily utilized in processed foods, accounting for the vast majority of the excess sodium consumed throughout the world. Though discovered and utilized as a food additive later than sodium, phosphorus-based food additives have taken on a similar wide berth of uses, including as food preservatives and taste enhancers. Like sodium, phosphorus additives have become nearly indispensable in food manufacturing, substantially augmenting the phosphorus content of processed foods. The public health consequences of these trends have been well-publicized, particularly with respect to the link between excess dietary sodium intake and the increasing prevalence and severity of hypertension in both the developed and developing world. These trends have more ominous implications for millions of individuals living with chronic kidney disease (CKD), who have reduced capacity to excrete even normal dietary sodium and phosphorus loads. This review will focus on the impact of sodium- and phosphorus-based food additives on total daily intake of sodium and phosphorus in contemporary diets, the special implications this may have for individuals with chronic kidney disease, and potential strategies for reducing the consumption of sodium and phosphorus-based food additives in CKD patients.

Sodium Additives

Sodium-based food additives were introduced into the human diet somewhere between 5,000 to 10,000 years ago when they were found to retard the spoilage of poultry and meat products.[1] This discovery revolutionized the capacity for early societies to preserve meat for personal consumption and/or trade purposes, markedly increasing the use of sodium in a variety of foodstuffs. The importance of this discovery is evident from historical records which show that access to salt was a cherished commodity in early societies, on par with the finest measures of wealth and social standing, and in some cases, used as a form of currency.[1, 2]

Historically, the primary reason to add sodium to foods was as a method for food preservation,[1] based largely upon sodium's antimicrobial properties.[3] With the advent of refrigeration and other advances in food preservation, the primary motivations evolved beyond just anti-spoilage agents to enhancing the taste and palatability of foods.[4] Salt (hereby referring to sodium chloride) has a number of desirable effects on foodstuffs, including improving the intensity of flavor and augmenting the overall perception of product thickness and fullness.[5, 6] Consistent with this, there is remarkable congruity with respect to the excessive levels of sodium consumption across countries with very different culinary traditions,[7, 8] suggesting a strong salt preference in human populations.[9] Along with its preservative and taste-enhancing effects, salt is also commonly used in the fermentation, emulsification, leavening, and enhancement of foods,[10] contributing to very high levels of salt usage by the food manufacturing industry.

Since most food items contain relatively low amounts of sodium naturally, the introduction of sodium additives into human food supplies effectively increased the average daily consumption of sodium from less than 400 mg per day in pre-historic times to an average of 4,000 mg per day in modern times, far above current recommendations for daily intake (**Table 1**).[8, 11] It is estimated

that only 10% of daily salt intake in Western populations comes from natural sources, whereas 75% comes from salt added to processed foods by manufacturers, and the remaining 15% from salt added during cooking or other discretionary uses.[12] While Asian populations manifest similarly high levels of added sodium intake,[8] there is important variability in the sources of added sodium in Eastern vs. Western countries. This was perhaps best demonstrated in the INTERMAP study, a large international cooperative study that estimated the quantity and sources of sodium intake in 4,680 individuals 40 to 59 years of age from Japan, the People's Republic of China, the United Kingdom and the United States.[13] This study showed that the majority of sodium intake in the United Kingdom and the United States came from processed breads, cereals, grains, meats, sauces and canned items with only a very small fraction (5 - 10%) coming from salt added in home cooking or at the table.[8] In contrast, the majority of salt intake in Japan came from soy sauce, salted fruits and vegetables, miso soup, and fish, whereas in China, the vast majority of sodium intake (76%) came from salt added during home cooking or at the table. These differences highlight the importance of regional factors in determining the sources of sodium intake in the developed and developing world.

Table 1

United States Department of Agriculture Dietary Reference Intakes for sodium and phosphorus intake by age group

Nutrient	Age	RDA/AI (grams/day)	TUL (grams/day)
Sodium[66]	0-6 months	0.12*	ND
	7-12 months	0.37*	ND
	1-3 years	1.0*	1.5
	4-8 years	1.2*	1.9
	9-50 years	1.5*	2.3
	50-70 years	1.3*	2.3
	> 70 years	1.2*	2.3
Phosphorus[37]	0-6 months	0.1*	ND
	7-12 months	0.28*	ND
	1-3 years	0.46	3.0
	4-8 years	0.5	3.0
	9-13 years	1.25	4.0
	14-18 years	1.25	4.0
	> 18 years	0.7	3.0

RDA, recommended daily allowance: defined as the average daily intake level sufficient to meet the nutrient requirements of nearly all (97-98%) healthy individuals in a group, calculated from the estimated average requirement (EAR) per day—if an EAR is not available because of lack of sufficient scientific evidence, an adequate intake level is developed instead; AI, adequate intake: defined as the recommended daily intake level based on observed or experimentally determined approximations of estimates of nutrient intake by a group (or groups) of apparently healthy people that are assumed to be adequate; TUL, tolerable upper limit: defined as the highest average daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population.[37]

*Represents AI (RDA unable to be determined)

Health Impact of Sodium Additives in Individuals with Chronic Kidney Disease Large observational studies have shown that excess salt intake is associated with adverse health outcomes among individuals with normal kidney function, including hypertension, cardiovascular disease events and excess urinary albumin excretion.[14-17] Randomized trials have largely corroborated these relationships,[18-20] most notably the Dietary Approaches to Stop Hypertension (DASH)-Sodium Collaborative Research Group that showed that diets low in sodium significantly reduced blood

pressure in study participants.[21] These findings are in line with animal data showing that excess dietary sodium intake increases systemic blood pressure, induces left ventricular hypertrophy and promotes vascular damage.[15, 22]

The adverse effects of excess dietary sodium intake are magnified in individuals with CKD. Much like individuals with normal kidney function who are classified as "salt sensitive,"[23] individuals with CKD have impaired neurohormonal mechanisms for enhancing excess sodium excretion in the urine, resulting in maladaptive increases in systemic blood pressure, renal plasma flow, and ultimately glomerular filtration pressure.[24, 25] All of these factors, in turn, strongly contribute to the development of hypertension, vascular injury, and their sequelae including proteinuria and progression of renal failure, in CKD patients.[2, 26] Since sodium additives make up the lion's share of excess sodium consumption in the food supply, reducing the intake of sodium additives is paramount to improving cardiovascular and renal outcomes in CKD patients consuming a typical Westernized diet.

Regulation of Sodium Additive Use Since only a small fraction of sodium consumed on a daily basis comes from discretionary sodium use (with the notable exception of the People's Republic of China), sodium additives in processed foods represent the single greatest barrier to lowering sodium intake in CKD patients, particularly those who do not have the financial means to purchase fresh foods. As such, any serious public health efforts to reduce the intake of sodium in CKD patients will have to include a strategy for reducing the use of sodium additives by the food manufacturing industry.

In order to understand the key regulatory barriers to attaining this goal in the US, it is helpful to review some of the legal framework underlying food additive regulation. Much of the framework is based upon the 1958 Food Additives Amendment (FAA) to the Federal Food, Drug, and Cosmetic Act of 1938.[27] In brief, this amendment defined any substances intentionally added to food by manufacturers as "food additives," and required manufacturers to obtain approval from the Food and Drug Administration (FDA) prior to adding these substances to food (it should be noted at this juncture that the legal definition of a "food additive" as established by the FAA differs quite a bit from the more colloquial uses of the term—for this reason, food additives will be put in parentheses when referring to the legal sense of the term here on out). This approval included the requirement that substances meet the relatively steep safety standard of "reasonable certainty of no harm" under the conditions of its intended use. Importantly, however, substances that were used in ways generally recognized as safe (GRAS) or that were used in ways previously sanctioned by the FDA or the Department of Agriculture prior to the enactment of the FAA were excluded from this definition. This is critical in that most uses of salt at that time (and continuing through today) were able to be excluded from the definition of a "food additive" under these provisions, exempting salt and other sodium-based ingredients from undergoing the stringent pre-market reviews of safety required for "food additives" by the FAA.

Recognizing the importance of reviewing the GRAS status of substances over time, the FDA in 1969 designated a Select Committee on GRAS Substances (SCOGS) to review the safety profile of all current GRAS substances (including salt).[10] The findings of this report raised substantive concerns about whether salt met the "reasonable certainty of no harm" safety standard, which could

put it status as a GRAS substance in peril and thus, subject it to greater regulation. However, the FDA did not modify the status of salt after reviewing the results of the report, saying in essence that it did not have enough evidence to overturn its GRAS status.[10] There have been further attempts to reduce salt intake over the past 32 years, including a publication of a "Policy Notice" in 1982 in which the FDA called for a reduction in salt in processed foods through public education, voluntary industry efforts, and expanded disclosure of sodium content on product labels.[10] More recently, the FDA has proposed to mandate the listing of sodium content of foods in fast food establishments and restaurants in order to make it easier for consumers to identify lower sodium options.[10] In addition, a 2010 Institute of Medicine report detailed a number of strategies to gradually reduce sodium content of processed foods over time.[10] To date, however, these efforts have led to only marginal reductions in sodium additive intake in the US.[28]

Phosphorus Additives

Dietary phosphorus consists of both "organic" sources of esterified phosphorus, such as meats, dairy products and vegetables, and "inorganic" forms of phosphorus that are commonly added to processed foods and beverages.[29-31] Unlike sodium, organic or natural forms of phosphorus are plentiful in the food supply, making up the majority of phosphorus consumed on a daily basis.[32] However, phosphorus-based additive use exploded during the 20th century,[33] substantially augmenting total phosphorus intake in modern diets.

Phosphorus-based additives serve a number of critical functions for food manufacturing, including pH stabilization, metal cation sequestration, emulsification, leavening, hydration, and bactericidal actions, among others.[33] Because of this wide diversity of applications, the use of phosphorus additives in the food manufacturing industry is immense—for example, over 40 million pounds of phosphorus additives were used annually in the US during the 1970's by the meat industry alone,[33] a figure that has likely grown over the past 40 years as demand for convenience and fast foods has increased. The magnitude of the use of phosphorus additives in the meat industry pales in comparison to that of the baking industry, which utilizes the highest quantities of phosphorus additives because of the key role that phosphorus acids play as dough leavening agents.[34] In a report commissioned by the U.S. Department of Commerce in 1972, baked goods were estimated to contain nearly 10-fold higher amounts of phosphorus additives than meat products.[35] Phosphorus additives, including those complexed with sodium, are also commonly used in milk and dairy products (particularly processed cheeses), seafood, and beverages. Dark colas and sodas in particular are the beverages that contain the highest amounts of phosphorus additives, principally in the form of phosphoric acid.[36]

Most individuals in the U.S. easily receive—and in fact usually exceed—the recommended daily allowance (RDA) of dietary phosphorus. Although the current RDA for phosphorus is 700 mg per day for adults (Table 1),[37] the most recent estimates of average daily intake for US adults 20 years of age and older is ~1550 mg for males and ~1120 mg for females, due in large part to the high intake of phosphorus-rich foods in the American diet.[38] The nearly ubiquitous distribution of phosphorus additives in processed foods augments phosphorus intake even further,[39] with estimates ranging from 250 to 1,000 mg of extra phosphorus per day.[40-42] should be noted, however, that some of the studies from which these estimates were derived have important limitations. For

example, in one highly-cited study, healthy volunteers were fed a balanced diet consisting of additive-free food for four weeks, after which they were fed a diet that looked virtually identical with the only difference being that instead of being additive-free, the foods were additive-rich.[40] The measured content of phosphorus in the additive-rich diet was approximately 1,000 mg higher per day than in the additive-free diet, suggesting that additive-enhanced foods can nearly double total phosphorus intake per day. However, the meat products used as additive-rich foods in this study were manufactured using quantities of phosphorus additives nearly twice that normally used by the meat industry,[33] likely exaggerating the difference in phosphorus content between the diets. Furthermore, the study was specifically designed to accentuate the differences between an additive-free and an additive-rich diet, and thus, may not be representative of more real-world scenarios in which individuals are consuming a mixture of both. Nevertheless, irrespective of the exact quantity, studies have shown that phosphorus additives can substantially increase phosphorus contents of processed foods.[29, 32, 43]

Importantly, despite their widespread use, phosphorus additives are typically unaccounted in the estimated phosphorus content of processed foods because food manufacturers are not required to list their quantities.[31] Thus, not only do phosphorus additives increase daily phosphorus intake, they represent a largely "hidden" dietary phosphorus load in typical American diets. This is noteworthy in that phosphorus additives are absorbed with much greater efficiency in the gut (> 90%) than organic forms of phosphorus in animal or vegetable proteins (~50-60%), with potentially important consequences.[31] Indeed, a study showed that foods with higher phosphorus bioavailability significantly increased serum phosphate and fibroblast growth factor 23 (FGF23) concentrations in CKD patients,[44] suggesting that the high bioavailability of phosphorus additives may potentiate their adverse impact on phosphorus homeostasis in CKD.

Health Impact of Phosphorus Additive Use in CKD patients Unlike sodium, data on the health impact of phosphorus additives are sparse in the general population, and nearly non-existent in individuals with kidney disease. Although a number of studies have examined the adverse effects of oral phosphate supplement loading in healthy volunteers,[45-47] supplement loading does not take into account the effects of food processing or cooking on the biochemical properties of food additives, making it unclear how well these studies captured the physiological effects of commercial food additives in humans. The few studies that did examine the effects of additives found in commercially-processed foods were primarily done in healthy female volunteers, and in general showed that high phosphorus additive intake promoted bone loss, partly though disruptions in calcium balance.[48-54] Whether high phosphorus additive intake has adverse effects on blood pressure or kidney function in healthy individuals has not been studied in detail and should be the focus of future investigation.

To date, no physiological studies have specifically examined the impact of commercially-derived phosphorus additives on bone and mineral metabolism in individuals with CKD. However, one study did examine the impact of lowering phosphorus additive intake on serum phosphate concentrations in hemodialysis patients. In this study, maintenance hemodialysis patients were taught how to read product labeling while grocery shopping in order to avoid purchasing items containing phosphorus additives and how to make better choices in choosing low-phosphorus options when eating at local fast food restaurants.[55] After three months of the intervention, mean serum

phosphate concentrations declined by 1.0 mg/dl in patients who received the intervention as compared to 0.4 mg/dl in control patients who did not (*P* for difference 0.02), suggesting a modest benefit of avoidance of phosphorus additives in hemodialysis patients. The extent to which avoidance of phosphorus additives improves phosphorus homeostasis in pre-dialysis CKD patients consuming typical Westernized diets is unclear and should be the focus of future studies.

Regulation of Phosphorus Additive Use In recognition of the already high intake of natural forms of phosphorus in modern diets, several regulatory agencies—most notably the Joint Food and Agriculture Organization /World Health Organization Expert Committee on Food Additives (JEFCA) and the aforementioned SCOGS from the FDA—commissioned separate studies to assess the safety of phosphorus additives in processed foods. The JEFCA report, released in 1964, evaluated all available studies examining acute and chronic toxicities of high phosphorus intake.[56] The main findings of the report were that phosphorus compounds commonly used as food additives at that time appeared to be safe for public consumption as long as they were not ingested in excess amounts. To aid in determining what would constitute excess amounts, the committee recommended upper limits of daily phosphorus additive intake deemed to be safe for healthy populations. Two thresholds were recommended—an "unconditional zone of acceptability" and a "conditional zone of acceptability." The unconditional zone (30 mg/kg a day or 2,100 mg/day in a 70 kg person) represented the level of phosphorus additive use that was deemed effective for the intended purpose of the additive and could "be safely employed without further expert advice," for example from a panel of nutrition specialists.[57] The conditional zone (30 to 70 mg/kg day) represented levels that could be used safely in the community, but which should have some level of expert supervision that could be readily available for direction or advice.

Like the JEFCA report, the 1975 SCOGS report reviewed many of the same studies from the 1950's through the early 1970's, and came to the conclusion that phosphorus-based food additives posed little threat to consumer safety when used in quantities that "are now current or might reasonably be expected in the future."[58] As such, the FDA kept phosphorus additives among the group of GRAS substances, saying in summary, that "None of the GRAS phosphates is intrinsically harmful and their use in foods does not present a hazard when the total amount of phosphorus ingested and the intakes of calcium, magnesium, vitamin D and other nutrients are satisfactory."[58]

While it is possible that phosphorus additives are safe for public consumption when used under these conditions, critical limitations in the literature used to derive these recommendations should prompt caution before drawing this conclusion. First, the vast majority of animal studies cited by these reports were conducted in the 1960's and 1970's, 20 – 30 years before the biological basis for a direct link between excess phosphorus and cardiovascular disease (ie, vascular calcification) was first reported.[59] As a result, while renal and bone toxicities were carefully evaluated in these studies, the impact of excess phosphorus intake on cardiovascular health was examined in much less detail. Moreover, critical hormones involved in phosphorus homeostasis, most notably FGF23, were unknown in that era. FGF23 is a novel phosphaturic hormone that is stimulated by increased dietary phosphorus intake.[60] High FGF23 concentrations have been strongly associated with cardiovascular disease, including vascular calcification, endothelial dysfunction and left ventricular hypertrophy.[61-64] Since FGF23 was not discovered until the beginning of this century,[65] none of these older studies examined the potential adverse effects of phosphorus additives on FGF23 se-

cretion. Finally, very few of these studies were conducted in humans. This is a critical gap in the literature given that phosphorus toxicology research in animals rarely accounts for food processing conditions such as cooking, which may modify the biochemical properties of food additives.[33] For all these reasons, the full public health implications of the high use of phosphorus additives in the food manufacturing industry remain largely unknown.

Sodium and Phosphorus-based Food Additives: Assessing the Forks in the Road

As the above discussion makes clear, addressing the high use of the additives in processed foods is critical for meaningfully reducing sodium and phosphorus intake in the general population, and CKD patients in particular, since these foods constitute such a large proportion of what most individuals consume. Although a comprehensive review of all the steps needed to arrive at this objective is beyond the scope of this review, several key points will be emphasized below.

First, any federally-mandated reductions in sodium will likely require either revoking sodium's GRAS status (i.e., re-classifying it as a "food additive"), or altering sodium's GRAS status to require more stringent safety standards, including limitations in the quantities that can be added to food. Both maneuvers would likely hinge on being able to convince the FDA (and other powerful political interests) that sodium-based additives violate the "reasonable certainty of no harm" safety standard, and as such, require greater monitoring and regulation. Unfortunately, this is not straight-forward, as there are a number of practical and legal hurdles that would need to be overcome to accomplish this goal (reviewed in-depth in reference [10]). Nevertheless, the large and growing body of evidence showing that high sodium intake poses a real and present public health danger would form a strong foundation for sustaining such an effort. The same cannot be said about phosphorus-based food additives. Indeed, as mentioned above, data on the impact of phosphorus additives in humans is limited and/or largely extrapolated from animal studies over forty years old. Therefore, before the safety of phosphorus additives can be reasonably challenged, more studies are needed to determine the full impact of these additives on mineral metabolism and cardiovascular health.

Second, any efforts to reduce sodium additives in processed foods, whether by federal mandate or public education programs, will likely fail without addressing the strong salt preference in human populations. Indeed, the single greatest barrier to the voluntary reduction in the use of sodium additives by the food industry has been the well-founded fear that doing so would drive consumers to higher-sodium-containing products made by competitors.[10] Because of this, any sustainable reductions in sodium additive use will likely require slow, step-wise, and across-the-board decreases in sodium content so that consumers gradually become accustomed to lower sodium intake, with no manufacturer gaining a competitive edge over another. Whether similar issues apply to phosphorus additives is less clear. However, given phosphorus additives' diversity of applications in improving the taste, appearance, and shelf-life of foods, it is very possible that consumer preferences could also curtail efforts to reduce their use if these additives were lowered in too rapid or uncoordinated a manner.

Third, it will be quite important to mind the "law of unintentional consequences" in the process of implementing any of these initiatives. Indeed, it is quite ironic that previous attempts to reduce the content of sodium in food additives may have inadvertently increased the use of phosphorus additives. As postulated by one authority in the field of phosphorus additives, interest in the use of these additives in meat products spiked in the 1980's in response to several position papers from the US National Academy of Sciences calling for reductions in the use of sodium as food additives.[33] This is because phosphorus can replace many of the functions of sodium in food processing, making phosphorus additives natural alternatives to sodium, and potentially accounting for the increase in the use of these additives in the US over the past 30 years.[50] As another sobering example, efforts to reduce salt added to ready-to-eat foods in the United Kingdom were linked to an outbreak of listeriosis from 2001 to 2005.[10] Given sodium's strong anti-microbial actions against pathogens such as *Clostridium botulinum* and *Listeria monocytogenes*, it will be important to understand the safety implications of reducing sodium or phosphorus in processed foods before additive-lowering programs are widely adopted.

Though formidable, none of these barriers are insurmountable. As any sustainable in-roads in reducing sodium and phosphorus intake in modern diets will require a coordinated action at all levels, it is hoped that by having a better understanding of the scope of the issue, how it uniquely impacts CKD patients, and the major impediments in resolving the situation, the nephrology community can better focus its energy and efforts in successfully working with industry, the government, and, most importantly, patients, to achieve these goals. Given that nutrition plays such a key role in CKD outcomes, these issues should be among the highest priorities in the research and clinical community.

CLINICAL SUMMARY

- Sodium and phosphorus-based food additives have a wide diversity of applications in processed food, making them heavily utilized in the food manufacturing industry.
- The proportion of daily sodium and phosphorus intake that comes from food additives alone is substantial, and in the case of sodium, accounts for nearly 75% of total sodium intake per day in Westernized diets.
- Excess sodium and phosphorus intake have important links to cardiovascular and bone disease in chronic kidney disease, making food additives a major nutritional risk factor for adverse clinical outcomes in individuals with chronic kidney disease.
- Since current laws classify sodium and phosphorus-based food additives as generally safe for public consumption—essentially allowing them to be used with little to no restrictions by the food industry—this represents a major barrier to reductions in intake of excess sodium and phosphorus in individuals with chronic kidney disease.

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Footnotes

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Sodium Reduction

On this page:

- At a Glance: Lowering Sodium in the Food Supply
- Frequently Asked Questions on FDA's Sodium Reduction Strategy
- Consumer Information and Additional Resources
- Guidance for Industry

Lowering Sodium in the Food Supply

The Problem

- The majority of sodium consumed comes from processed, packaged and prepared foods, not from table salt added to food when cooking or eating. This makes it difficult for all of us to control how much sodium we consume.
- Some companies have reduced sodium in certain foods, but many foods continue to contribute to high sodium intake, especially processed, packaged and prepared foods, including foods eaten away from home.

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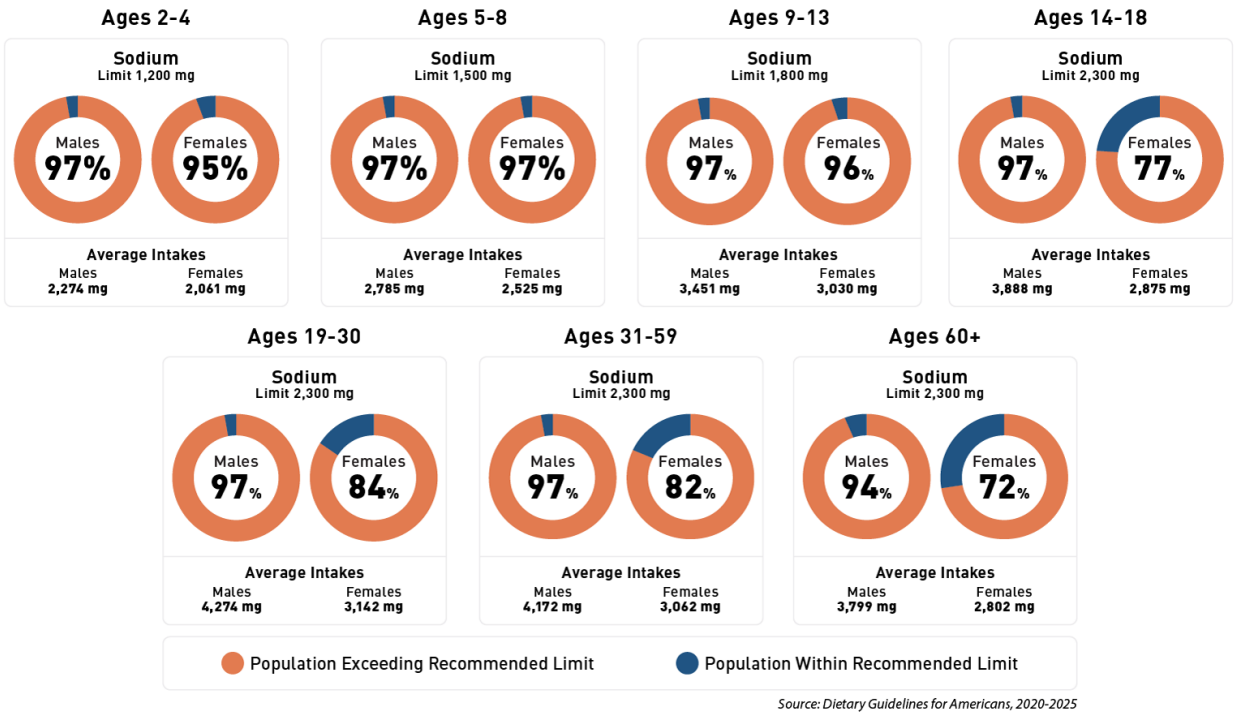
The Public Health Need

- Americans consume on average 3,400 milligrams (mg) of sodium per day—nearly 50%more than the 2,300 mg limit recommended by federal guidelines for people 14 years and older. Recommended limits for children 13 and younger are even lower.
- Most children and adolescents also eat more sodium than is recommended.
- Too much sodium can raise blood pressure, which is a major risk factor for heart disease and stroke.
- More than 4 in 10 American adults have high blood pressure and that number increases to almost 6 in 10 for non-Hispanic Black adults. Additionally, about one in 10 children (8-12 years) and one in 8 teens (13-17 years) has elevated or high blood pressure.
- Reducing sodium intake has the potential to prevent hundreds of thousands of premature deaths and illnesses in the coming years.

Population Exceeding Recommended Sodium Limit

Americans consume more sodium than is recommended. The following are average daily intakes by age, relative to recommended limits.



Source: Dietary Guidelines for Americans, 2020-2025

Enlarge in PDF (/media/152751/download?attachment)

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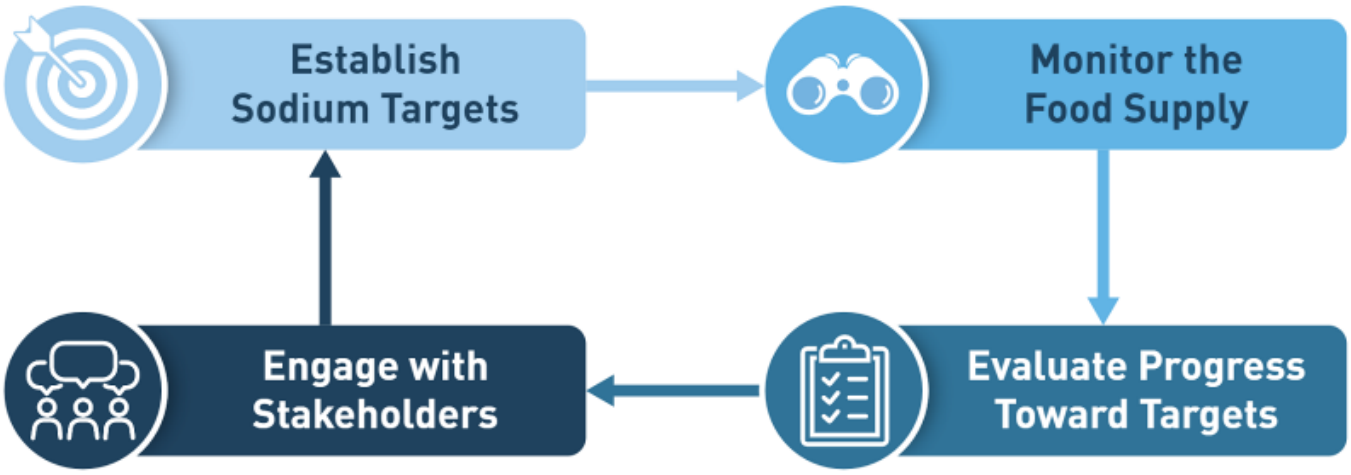
The Science

- Strong scientific evidence supports lowering sodium intake from current levels.
- The science supporting the relationship between sodium reduction and health is clear: When sodium intake increases, blood pressure increases and high blood pressure is a major risk factor for heart disease and stroke – two leading causes of death in the U.S.
- The FDA's goal to reduce sodium intake is consistent with the Dietary Guidelines for Americans, 2020-2025 (https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials) and the 2019 National Academies of Sciences, Engineering, and Medicine Dietary Reference Intakes Report on Sodium and Potassium. (https://www.nap.edu/read/25353/chapter/1) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

The FDA's Approach

To gradually reduce sodium across the food supply, the FDA is taking an iterative approach that includes establishing voluntary sodium targets for industry, monitoring and evaluating progress, and engaging with stakeholders.



Final Guidance

- The FDA issued the final guidance with voluntary targets for reducing sodium (/regulatory-information/search-fda-guidance-documents/guidance-industry-voluntary-sodium-reduction-goals) in commercially processed, packaged and prepared food over the next 2.5 years. The approach supports sodium reduction efforts already made by industry, provides common targets for defining and measuring progress, and provides companies with the flexibility and time to meet these targets.
- The FDA's approach encourages a level playing field by setting voluntary targets for both processed and restaurant foods.

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- To achieve a significant impact, the FDA is especially encouraging adoption by food manufacturers whose products make up a significant proportion of national sales in one or more categories and restaurant chains that are national and regional in scope.

Voluntary Targets

- There are 16 overarching categories with individual sodium targets for 163 subcategories of food in recognition that a one-size approach does not fit all.
- The targets in the final guidance are designed to support decreasing average daily sodium intake by about 12 percent—from approximately 3,400 milligrams (mg) to 3,000 mg.
- The targets take into consideration the many functions of sodium in food, including taste, texture, microbial safety and stability. The targets do not address naturally occurring sodium or salt that individuals add to their food.

Next Steps

- The FDA will monitor the sodium content of the food supply, evaluate progress towards achieving the targets in the final guidance and engage with stakeholders on sodium reduction efforts and the targets.
- Based on that information, the FDA expects to issue revised subsequent targets in the next few years to facilitate a gradual, iterative process to reduce sodium intake.

Frequently Asked Questions on FDA's Sodium Reduction Strategy

What is the FDA doing?

Americans are consuming too much sodium in their diet, and the majority comes from processed, packaged and prepared foods, not the salt shaker. That is why we developed the final guidance with sodium reduction targets to encourage industry to gradually reduce sodium in a wide range of foods over the next 2.5 years.

Which foods are highest in sodium?

Sodium is added to almost all processed, packaged and prepared foods. Some individual foods are known to be high in sodium, but it’s also important to consider how often the food is consumed. Other foods may be lower in sodium, but are often consumed in greater amounts and/or more frequently. Commonly consumed foods such as deli-meat sandwiches, pizza, burritos and tacos, soups, savory snacks, pasta dishes, burgers and egg dishes are known to

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contribute significantly to sodium intake. Some high-sodium foods, such as dried fish, do not contribute as much to overall sodium intake because they typically aren't consumed in large quantities, or as often.

Why is sodium added to food?

Sodium is added to processed, packaged and prepared foods for a wide variety of reasons. For example, it is used to control microbial growth, which can cause food to spoil and can cause foodborne illness. Sodium also is used to improve flavor and texture, and for baking and curing meat. While sodium is necessary for many reasons, today's food supply contains too much sodium.

Why is reducing sodium in foods important?

Too much sodium contributes to high blood pressure, which can lead to heart attacks and strokes. Americans now consume on average about 3,400 milligrams (mg) of sodium each day, while federal guidelines recommend less than 2,300 mg per day for people 14 years and older. Recommended limits for children 13 years and younger are even lower. Reducing sodium in foods could prevent hundreds of thousands of premature deaths and illnesses over a decade.

How strong is the science on the benefits of sodium reduction?

Strong scientific evidence supports lowering sodium intake from current levels. Excess sodium intake increases risk for high blood pressure, heart disease and stroke. The Dietary Guidelines for Americans, 2020-2025 recommends limiting sodium intake to 2,300 mg per day for people 14 years and older; and even less for those 13 years and younger.

What if I don't have these health problems?

More than 100 million American adults have high blood pressure, and blood pressure generally rises as you get older. This tendency for blood pressure to rise with age is seen mostly in western countries where sodium intakes are high. Children and adolescents also are more likely to have increased blood pressure with higher sodium intakes. Studies suggest that the preference for sodium is affected by early life consumption habits and can extend into adult years, although palates can also adjust to lower sodium in foods.

Can't people just check the labels on foods in the supermarket?

Consumers can, and should, check labels when they are available, but a few types of foods do not require the Nutrition Facts label. An example is deli meats you buy at a counter. Even with labeling, consumers still have a difficult time eating the recommended amount of sodium because sodium levels in today's overall food supply are just too high. The majority of the sodium we eat comes from processed, packaged and prepared foods, not from table salt added to food when cooking or eating.

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Why are you including restaurant foods?

Americans eat about one-third of their food calories and spend about half of their food dollars outside the home, so it's important that restaurants are part of the solution, along with the rest of the food industry. Including restaurant foods is necessary to achieve sodium reduction goals and for people to adapt their taste buds whether they are eating at home or outside the home.

Won't foods with less sodium taste bad?

The sodium in your diet comes from a lot of different types of foods—especially mixed dishes that have many components and sauces. Our approach is to encourage reductions in a variety of products—not just ones that are especially high in sodium. This way, we aren't recommending drastic reductions that will significantly affect the taste of food. We carefully studied the range of popular foods in today's marketplace to see what reductions are possible based on what some companies are already doing and what is selling well in the marketplace.

We also know that people usually don't notice small reductions (about 10 percent) in sodium. And, over time, people's taste buds get used to these changes, especially if they are made gradually. In addition, there are other ways companies can reformulate, or change, certain foods while still making them appealing to consumers. Examples include adding savory herbs and spices, salt blends or other flavorings in place of sodium.

Haven't many companies already come out with lower sodium foods?

Yes, some food companies are making progress already and we applaud their leadership. But even with these efforts, the sodium content of the food supply remains high. Part of the problem has been the focus on making a few foods very low in sodium, instead of making most foods a little lower in sodium. We want to give the industry common targets across a broad range of foods.

When will I see changes in sodium in the foods I buy?

We are encouraging companies to meet short-term targets in two and a half years (note that some foods already meet the short-term targets). We expect that if the food industry reaches these initial targets more broadly, it would reduce average sodium intake to about 3,000 mg per day.

Are other countries making similar efforts to reduce sodium in foods?

Yes. There are 96 countries working to reduce the sodium intake and 48 have set sodium target levels for one or more processed foods. The World Health Organization rates sodium reduction as a "Best Buy" to improve public health. It is difficult to compare countries in terms of progress

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because sodium intake varies worldwide, and different approaches may be needed based on foods typically eaten. But many countries, such as the United Kingdom and Canada, have made progress on sodium reduction with approaches similar to that being used here.

How will you know if companies are making progress in reducing sodium?

A key part of the FDA's sodium reduction plan is to monitor progress toward our goals on a regular basis to understand changes that are occurring. We will work with other government agencies, such as the U.S. Department of Agriculture and the Centers for Disease Control and Prevention on these monitoring efforts. The FDA also plans to actively engage with food manufacturers to learn about their sodium reduction efforts.

Consumer Information on Reducing Sodium Intake

- Sodium on the Nutrition Facts Label (/food/nutrition-education-resources-materials/sodium-nutrition-facts-label)
- Sodium Intake and Health (https://www.cdc.gov/salt/)
- Cut Down on Sodium (health.gov) (https://health.gov/sites/default/files/2021-08/DGA_SodiumFactSheet_2021-05-26_508c.pdf)

Guidance for Industry

- Guidance for Voluntary Sodium Reduction Goals (/regulatory-information/search-fda-guidance-documents/guidance-industry-voluntary-sodium-reduction-goals)
- Food Categories and Voluntary Targets for Sodium Reduction (Final Guidance Appendix Table 1) (/media/98277/download?attachment) (XLSX: 47KB)
- Summary Explanation of Food Categories and Final Voluntary Targets for Sodium Reduction (Appendix Table 1) (/media/98552/download?attachment) (PDF: 686KB)
- Notice of Availability for the Final Guidance (https://www.federalregister.gov/public-inspection/2021-22453/guidance-voluntary-sodium-reduction-goals-target-mean-and-upper-bound-concentrations-for-sodium-in)

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- Docket Folder FDA-2014-D-0055 (https://www.regulations.gov/docket/FDA-2014-D-0055)
    - Reference 05 - Supplementary Materials Packet re Voluntary Sodium Reduction Goals (https://www.regulations.gov/document/FDA-2014-D-0055-0011) (Previously Reference 17 in Draft Guidance)
    - Reference 06 - Survey of Micro Issues in FDA Reg Products (https://www.regulations.gov/document/FDA-2014-D-0055-0008) (Previously Reference 18 in Draft Guidance)
    - Reference 07 - Survey of Micro Issues Meat and Poultry Products (https://www.regulations.gov/document/FDA-2014-D-0055-0100) (Previously Reference 19 in Draft Guidance)
    - Reference 08 - Salt Taste Preference and Sodium Alternatives (https://www.regulations.gov/document/FDA-2014-D-0055-0152) (Previously Reference 20 in Draft Guidance)
    - Sodium in the US Food Supply for Products in 2010 (https://www.regulations.gov/document/FDA-2014-D-0055-0559)
- *Constituent Update* Announcing the Sodium Reduction Final Guidance (/food/cfsan-constituent-updates/fda-issues-sodium-reduction-final-guidance)

Additional Information

- FDA To Propose to Permit Salt Substitutes to Reduce Sodium in Standardized Foods (/food/cfsan-constituent-updates/fda-propose-permit-salt-substitutes-reduce-sodium-standardized-foods) (March 2023)
- FDA Issues Draft Guidance on Dietary Guidance Statements on Food Labels (/food/cfsan-constituent-updates/fda-issues-draft-guidance-dietary-guidance-statements-food-labels) (March 2023)

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Contains Nonbinding Recommendations

Voluntary Sodium Reduction Goals: Target Mean and Upper Bound Concentrations for Sodium in Commercially Processed, Packaged, and Prepared Foods: Guidance for Industry

You may submit electronic or written comments regarding this guidance at any time. Submit electronic comments to https://www/regulations.gov. Submit written comments on the guidance to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this guidance, contact the Center for Food Safety and Applied Nutrition (CFSAN) at 240-402-1200.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition

October 2021

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Voluntary Sodium Reduction Goals: Target Mean and Upper Bound Concentrations for Sodium in Commercially Processed, Packaged, and Prepared Foods: Guidance for Industry

I. Introduction

This guidance is intended to provide measurable voluntary short-term (2.5-year) goals for sodium content[1] in commercially processed, packaged, and prepared foods[2] to reduce excess population sodium intake, while recognizing and supporting the important roles sodium plays in food technology and food safety.

Sodium is widely present in the American diet (most commonly, but not exclusively, as a result of eating or drinking foods to which sodium chloride, commonly referred to as "salt," has been added). More than 70 percent of total sodium intake is from sodium added during food manufacturing and commercial food preparation (Refs. 1, 2). Average sodium intake in the U.S. is approximately 3,400 milligrams/day (mg/day) (Ref 3). The *Dietary Guidelines for Americans, 2020-2025* (*Dietary Guidelines*) (Ref. 3) advises individuals 14 years and older to limit their consumption to 2,300 mg/day; this aligns with recommendations from the National Academies

[1] In this document, we refer primarily to "sodium," a component of sodium chloride, commonly known as "salt" (21 CFR 101.22(h)(4)). Most, but not all, sodium is added to food in the form of salt, and we are interested in all sources of sodium added to foods. The focus of this guidance is on foods to which sodium has been added, not those foods, such as milk, that contain only intrinsic sodium.

[2] "Commercially processed, packaged, and prepared foods" refers to processed, multiple-ingredient foods that have been packaged for direct sale to consumers, for use in food establishments including, but not limited to, restaurants, or for resale to other members of the food industry, as well as foods that are prepared by food establishments for direct consumption. The guidance addresses certain conventional foods, and not dietary supplements.

of Sciences, Engineering and Medicine (NASEM), which set the Chronic Disease Risk Reduction Intake (CDRR) for sodium at 2,300 mg/day[3] for those 14 years and older (Ref. 4).

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

A: Purpose and Scope

This guidance aims to help Americans reduce average sodium intake to 3,000 mg/day by encouraging food manufacturers, restaurants, and food service operations to gradually reduce sodium in foods over time. Although we recognize that a reduction to 3,000 mg/day still would be higher than the recommended sodium limit of 2,300 mg/day, the 2.5-year goals are intended to balance the need for broad and gradual reductions in sodium and what is publicly known about technical and market constraints on sodium reduction and reformulation. The guidance provides short-term goals that include both a target mean concentration and an upper bound concentration of sodium for various specified categories of food. The target mean sodium concentration is our goal for the food category as a whole rather than for every product in that category. The upper bound concentration is our goal for the highest sodium concentration for any product in that food category.

FDA recognizes the important role of sodium in food for microbial safety, stability, and other functions. FDA's approach to establishing these voluntary, short-term goals is grounded in research, review, and expert consultation (Refs. 5-9). The goals are intended to provide both FDA and the food industry with a common system for defining and measuring progress in reducing sodium. The goals are intended to complement existing efforts by food manufacturers, restaurants, and food service operations to achieve sodium reduction.

The voluntary sodium content goals in this guidance are intended to:

- Support increased food choice for consumers seeking a diverse diet that is consistent with recommendations of the *Dietary Guidelines* by encouraging food reformulation and new product development for Americans;
- Support the *Dietary Guidelines*, and NASEM CDRR recommendations of limiting sodium intake to 2,300 mg/day[4] by encouraging sodium reduction over the short term to achieve an average intake of 3,000 mg/day;

[3] Above this level, sodium intake should be reduced in order to reduce the risk for hypertension and cardiovascular disease; lower levels are recommended for children younger than 14 years of age (Ref. 4).

[4] The *Dietary Guidelines* recommendation is for individuals aged 14 and older to limit intake of sodium to less than 2,300 mg/day. The CDRR level for individuals ages 14 years and older set by the NASEM 2019 Dietary Reference Intakes for sodium and potassium report is 2,300 mg of sodium per day (Ref. 4). The recommendations for children younger than 14 years of age are the NASEM age- and sex-appropriate CDRRs.

- Provide uniform metrics (mg of sodium per 100 g of food) for voluntary sodium reduction for industry stakeholders;
- Focus on the total amount of sodium in a given food as opposed to individual sodium-containing ingredients; and
- Support and extend industry's voluntary efforts to reduce sodium across the range of commercially processed, packaged, and prepared foods.

The voluntary sodium content goals in this guidance are not intended to:

- Recommend specific methods and technologies for sodium reduction;
- Recommend how much of a sodium-containing ingredient, such as sodium chloride or sodium nitrite, should be used in a formulation (our recommendations focus instead on the total amount of sodium[5] in a given food);
- Focus on foods (e.g., milk) that contain only naturally occurring sodium; or
- Address the sodium chloride or other sources of sodium that individuals add to their food at the table or through cooking.[6]

B: Overview

This sodium reduction guidance is based on the following principles:

- Reduction in sodium levels should progress gradually to allow time for product reformulation;
- Population-level sodium intake reduction should progress at a pace such that consumer preferences and expectations for saltiness in foods adjust;[7]
- Reduction in sodium levels should not lead to reformulation that negatively affects the nutritional quality of the foods by modifying other nutrient levels (e.g., by increasing added sugars or saturated fat content) and should take into account all *Dietary Guidelines* recommendations and FDA policies;
- Population-level sodium intake reduction will involve ongoing voluntary efforts led by the food industry, in collaboration with FDA, our Federal partners, and other stakeholders;[8]
- Goals should be expressed in ways that support ongoing efforts to track modifications to the sodium content of the food supply over time;
- Successful sodium reduction is contingent upon broad participation by and distribution of impacts across the food industry; and

[5] We recognize that total sodium in a food may include some intrinsic sodium and that this contribution to the food's total sodium does not represent deliberate introduction of a sodium-containing ingredient. However, total sodium is the most practicable measure of the food's composition and is strongly correlated with the use of sodium-containing food ingredients in the foods that are the focus of this guidance.

[6] FDA supports public education efforts on how consumers can reduce sodium in their diet, including salt they add to their food.

[7] Consumer preferences and expectations for salty taste can adjust based on dietary changes (Ref. 8).

[8] This includes states, tribes, consumers, international governments, academic institutions, and other organizations as appropriate.

- Population-level sodium intake reduction can be advanced through both the categorization of the food supply based on relevant data and information (e.g., ingredient similarity, technical effects in the food, role in food safety, and range of sodium concentrations in marketed products) and the use of voluntary objectives.

C: FDA's Approach to Voluntary Sodium Reduction in the Food Supply

Multiple public health efforts have attempted to reduce sodium intake over the past 40 years (Ref. 10). However, these efforts, which mainly included education initiatives, have generally not been successful. The Institute of Medicine (IOM, now the Health and Medicine Division of NASEM) thus concluded that without an overall reduction of the level of sodium in the food supply, consumers will not be able to reach intakes recommended by the *Dietary Guidelines* (Ref. 10). As more than 70 percent of Americans' sodium intake comes from foods where sodium is added during food manufacturing and commercial food preparation (Refs. 11, 12), lowering population intake of sodium to more moderate levels must involve lowering the amount of sodium added to commercially processed, packaged, and prepared foods in the U.S. marketplace (Refs. 2, 10).

Various food manufacturers, retailers, and food service firms have initiated voluntary efforts to reduce sodium, with some success (Refs. 11, 12). However, consumers who are trying to consume less sodium continue to face significant challenges. The 2010 National Academies report "Strategies to Reduce Sodium Intake in the United States" noted that the food supply itself is a key obstacle for consumers: "The sodium densities of available foods—both in the marketplace and from restaurant/food service operations—make it difficult for consumers to meet dietary recommendations" (Ref. 10). Given the emphasis on sodium reduction by the public health community over the last several decades, the available evidence demonstrating little progress in reducing sodium intake on a population level over this time (Ref. 10), and the number of foods in the marketplace that are high in sodium, additional strategies are warranted to reduce sodium consumption. To assist consumers who want to lower the total sodium content of their diets, this guidance aims to support voluntary, coordinated, and gradual reduction of sodium across the food supply.

Below, we provide guidance to industry in the form of specific targets for a broad sector of the market for sodium content in categories of commercially processed, packaged, and prepared foods. These categories are compatible with existing industry and regulatory categories and with government databases (Ref. 5). This guidance is intended to inform general industry thinking about sodium content in their foods. This guidance is not intended to limit industry's use of any appropriate methods or technologies to achieve sodium reduction.

FDA, in cooperation with other agencies, intends to monitor the prevalence of sodium in the food supply over time using the measures described in this guidance and supporting documents. To avoid the potential for unintended consequences, we plan to monitor the levels of other nutrients (e.g., added sugars and saturated fat); such monitoring will be done by, for example, consulting product nutrition information and ingredient lists to ensure that no broad trends emerge that negatively affect the nutritional quality of foods. We will continue to discuss with industry the appropriate use of ingredients added to food as part of sodium reduction efforts

during product development or reformulation. Our goal is to encourage gradual, efficient reduction of overall sodium content using effective and sustainable strategies that maintain other measures of nutritional quality. Because many higher-selling products currently marketed are at or below the category means presented in this guidance, it should be possible to avoid disruptive changes to individual products that might result in noticeably altered taste, greatly reduced shelf life, or other undesirable product outcomes.[9]

D: Intended Audience

This guidance is intended for members of the food industry (e.g., food manufacturers and other establishments that commercially prepare foods), and also may be of interest to public health groups and consumers. Broad industry adoption of these voluntary recommendations can create a meaningful reduction in population sodium intake over time and support adjustment of consumer taste preferences. However, we recognize that most of the food consumption in the U.S. comes from a relatively small number of products and menu items in the marketplace that are produced by a limited number of food manufacturers. It is possible that reformulation by these food manufacturers could lead to increased demand for lower-sodium versions of ingredients used to produce packaged and prepared foods. As a result, such actions could help all members of the food industry be more readily able to provide lower-sodium products. Given the resources involved in successful reformulation to achieve voluntary sodium reduction and to have the most public health impact, we specifically encourage attention by:

- Food manufacturers whose products make up a significant proportion of national sales in one or more categories, and
- Restaurant and similar retail food chains that are national or regional in scope.

II. Background

A: Sodium and Health

Research shows that excess sodium consumption is a contributory factor in the development of hypertension (Refs. 4, 13-15), which is a leading cause of heart disease and stroke, the first and fifth leading causes of death in the United States, respectively (Ref. 16). Decreasing population sodium intake is therefore expected to reduce the rate of hypertension. Research also shows that the increase in blood pressure seen with aging, common to most Western countries, is not observed in populations that consume low sodium diets (Ref. 17) and that the U.S. population consumes far more sodium than recommended (Refs. 3 and 18). Moreover, dietary reduction of sodium can lower blood pressure, as has been demonstrated in the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (Ref. 19) and other experimental studies (Refs. 4 and 20).

[9] We provide information about products relative to category means on our sodium reduction webpage at www.fda.gov/sodiumreduction.

B: U.S. Sodium Intake and Recommendations

Currently, the average sodium intake for Americans 2 years and older is approximately 3,400 milligrams per day (mg/day) (Refs. 3, 18). The recommendations of scientific groups that are charged with examining the totality of the evidence, including scientific bodies, qualified experts and governments around the world, support limiting sodium intake to about 2,300 mg/day (Refs. 3, 4, 21-24). Ninety-six countries have implemented a national strategy for sodium reduction (Ref. 25). A systematic review evaluating the effects of sodium reduction in high-income countries found no evidence of adverse effects from initiatives to reduce sodium intake (Ref. 26).

This guidance supports the goal of reducing sodium intake as recommended by scientific consensus groups, by focusing on short-term reduction to 3,000 mg/day as a gradual approach to sodium reduction in the food supply. The guidance reflects the broad consensus among experts regarding the direct relationship between sodium and blood pressure, as well as the relationship between blood pressure and cardiovascular disease events (Ref. 4). With average sodium intake in the U.S. over 3,400 mg/day, there is considerable work to do to reduce intake to the recommended limit of 2,300 mg/day in order to reduce the risk of hypertension and cardiovascular disease. Thus, the overall goal of this guidance is to support reduction of average sodium intake to 3,000 mg/day as we continue the dialogue on sodium reduction.

C: Potential Public Health Impact of Sodium Reduction

Multiple studies have estimated the public health and economic benefits associated with broad reduction in sodium intakes in the U.S. (Refs. 27-30). Those studies have shown that reductions in average intake (modeled at a variety of intake levels below current intake, down to an average level of roughly 2,200 mg/day) have been estimated to result in tens of thousands fewer cases of heart disease and stroke each year, as well as billions of dollars in health care savings over time. One study (Ref. 27) used three epidemiological datasets to estimate the separate public health benefits of reducing the population's average sodium intake to 2,200 mg/day over 10 years. The researchers estimated that this pattern of reduction would prevent between 280,000 and 500,000 premature deaths over 10 years and that sustained sodium reduction would prevent additional premature deaths.

D: Other Initiatives with the Goal of Reducing the Sodium Content of Foods

This guidance is informed by domestic and international initiatives to reduce sodium in the food supply. In the United States, the New York City Department of Health and Mental Hygiene initiated the National Salt Reduction Initiative (NSRI),[10] a partnership of 70 local and state health departments and health organizations, to set voluntary targets to reduce sodium in restaurant and processed foods. The goal of NSRI was to decrease average sodium intake by 20 percent over five years (2009 through 2014) by developing stepwise reductions from 2009 base levels. More than 25 companies, including packaged food corporations and restaurants, responded to NSRI by committing to reductions in the sodium content of some of their products (Ref. 31). According to the most recent report, some participating food companies achieved the

[10] This initative was updated to the National Salt and Sugar Reduction Initiative (NSSRI) in 2019.

2012 NSRI targets for various categories (Ref. 11). By 2014, NSRI reported that 26 percent of packaged food categories met 2012 targets and 3 percent met 2014 targets (Ref. 12).

Internationally, of the 96 countries with sodium reduction strategies, more than 50 countries have developed initiatives to support the reduction of sodium in the food supply (Refs. 25, 32). These initiatives have included both voluntary and mandatory efforts. In an approach developed by the United Kingdom's (UK) Food Standards Agency, many companies voluntarily pledged to reduce sodium in their foods. The UK initiative resulted in a decline in average sodium intake from 3,800 to 3,240 mg/day between 2003 and 2011, and researchers concluded that decreases in blood pressure in the UK during this time were largely attributable to the reduction in sodium intake (Ref. 33). In 2020, the UK government issued revised voluntary targets to be achieved by 2024 (Ref. 34). Health Canada, the department within the Canadian government responsible for helping Canadians maintain and improve their health, also developed a voluntary approach to sodium reduction. Health Canada collated information from the food industry and other stakeholders to inform their "guiding benchmark" sodium reduction levels for processed foods, which were issued in 2012 to be achieved by 2016.[11] In 2017, Health Canada evaluated the food industry's efforts to meet sodium reduction targets in processed foods. Results showed that 52 percent of food categories met the Canadian Phase I, II, or III targets, indicating that voluntary efforts can reduce sodium in packaged foods (Ref. 35). In 2020, Health Canada also issued updated voluntary targets to be achieved by 2025 (Ref. 36).

E: Food Ingredient Regulation

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that a food additive be approved for use in food and used in accordance with its approved conditions of use (see generally 21 U.S.C. 348). Certain food substances are exempt from these requirements because they are exempt from the definition of a food additive. These food substances include substances that are generally recognized as safe (GRAS) for their intended use (see 21 CFR 170.30) and substances that have been prior sanctioned (21 U.S.C. 321(s)). FDA's food additive and GRAS regulations may establish certain limitations for the use of these food substances. Moreover, these regulations are predicated on usage of the substances under conditions of good manufacturing practices (21 CFR 170.30(h) and 21 CFR 172.5). In addition to the safety requirements of the FD&C Act, the intended use of a food ingredient in meat, poultry, or egg products must be verified as efficacious and suitable by the United States Department of Agriculture's (USDA's) Food Safety and Inspection Service (FSIS).[12] FDA regards salt (sodium chloride) as a common food ingredient that is GRAS for its intended use (see 21 CFR 182.1(a)), and salt (sodium chloride) is an optional or required ingredient in many food standard regulations promulgated by FDA or by USDA.[13]

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[11] Additional information on Health Canada's sodium reduction initiative can be found in FDA's Voluntary Sodium Reduction Goals: Supplementary Memorandum to the Draft Guidance (Ref. 5).

[12] Related Documents for FSIS Directive 7120.1 - Safe and Suitable Ingredients used in the Production of Meat, Poultry, and Egg Products, http://www.fsis.usda.gov/wps/portal/fsis/topics/regulations/directives/7000-series/safe-suitable-ingredients-related-document

[13] For discussions of FDA's regulation of sodium, see generally 72 FR 59973 (Oct. 23, 2007) and 47 FR 26590 (June 18, 1982).

III. Discussion

A gradual and voluntary approach to reducing sodium in the food supply is intended to create flexibility for industry members interested in supporting the public health goals of this guidance. By encouraging action with respect to the products that are the market leaders (i.e., products sold in the greatest numbers) in each category, we hope to stimulate innovative product reformulation that maintains market share while also having the most significant public health impact and minimizes the impact on low-market share products in the food category.

FDA has developed quantitative target mean concentrations and upper bound concentrations for sodium levels in various identified food categories. The target mean concentrations (target means) are goals for sodium levels for the category, calculated as the sales-weighted mean sodium level (in milligrams per 100 grams of food). In setting these target means, FDA has taken into account concentrations necessary to achieve important food safety functions (e.g., antimicrobial) and functionality roles. The short-term targets are intended to be feasible using existing technology and are within the range of currently available top-selling commercial products. The upper bound sodium concentrations (upper bounds) are goals for the highest level of sodium for products in each food category (in milligrams sodium per 100 grams of food).

In Table 1 in the Appendix of this guidance, we summarize the results of our analysis of the sodium content of the food supply and identify short-term target mean (average) sodium concentrations for a wide variety of food categories, as well as the upper bound sodium concentration for products in these food categories.[14] These sodium concentration goals were informed by the distribution of sodium from packaged products and menu items in the food supply in 2010, as well as by publicly available data and information about the formulation of sodium-reduced foods. Nutrition data came from Nutrition Facts labels for packaged foods and from restaurant nutrition information.[15]

Food industry manufacturers, particularly the firms described earlier (e.g., food manufacturers whose products make up a significant proportion of national sales in one or more categories and restaurants and similar retail food chains that are national or regional in scope), may consider using the voluntary goals in Table 1 to inform decisions about the use of sodium in products or menu items.

Table 1 contains four key elements:

- Foods and food categories;
- Baseline sodium concentrations;
- Target mean sodium concentrations; and

[14] See also FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for a detailed discussion of target and non-target categories of foods. Non-target categories of foods either did not contain meaningful amounts of sodium or did not contribute meaningfully to sodium intake in the general population because they were consumed rarely and thus provided little contribution relative to other food groups.
[15] Additional information on data sources is available in FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5).

- Upper bound sodium concentrations.

We describe each of these elements in more detail below.

A: Foods and Food Categories

In developing sodium reduction goals, FDA reviewed various food categorization systems,[16] identified significant contributors to the intake of sodium in the United States, and organized foods into various identified food categories. We identified and categorized the foods in these categories on the basis of:

- Contribution to sodium intake;
- The total amount of sodium in the food (foods with added sodium, i.e., not just naturally occurring);
- Similar functional roles for sodium-containing ingredients;
- Similar sodium concentrations;
- Similar technical potential for reduction in sodium content;
- Compatibility with existing industry and regulatory categories; and
- Comments received to the draft guidance docket.

Many food categories have recommended targets (listed in Table 1; e.g., various bakery products, meats, cheeses, and types of sauces, etc.). However, we did not suggest targets for certain categories that do not contribute meaningfully to overall sodium intake[17] (e.g., salted dried fish and organ meat) either because they were consumed rarely (by all ages and ethnicities) or because they provided little contribution to sodium intake relative to the other food groups.[18]

B: Baseline Sodium Concentrations

Table 1 presents baseline sodium concentrations for each of the identified food categories. Each baseline should be interpreted as our assessment of the approximate "state of the market" regarding sodium concentrations in each food category in 2010,[19] based on public representations of sodium content by the food industry through food labels and menus, rather than as representing a precise measurement of sodium concentrations in the food supply. We derived these baseline values from a large, market-weighted array of products in each category.

[16] The food categorization systems mentioned refer to various government food category systems, private-sector food category systems, and sodium reduction initiative category systems that are further described in the FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5).

[17] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for a table with foods for which targets were not developed, and Tables 1 and 2 of this guidance.

[18] For more detail about the process we used to identify and categorize these foods, see FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5), as well as our expanded definitions for categories in this guidance.

[19] For our rationale in selecting 2010 as our baseline year and for more detail about the data sources used, see FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5). For this guidance, baseline values for categories include the full year of 2010 data (Ref. 37).

We include them in the tables to provide context for the target mean concentrations and upper bound concentrations.

We developed the baselines for sodium concentrations using label data for packaged foods sold directly to the consumer and menu nutrition data for foods sold in large restaurant chains. We used these data because they are available for each individual product and they are the manufacturer's or restaurant chain's representation of the sodium content of their products. We also developed these baselines using sales volume data for the products involved, so that more widely consumed products in a category would have more influence on the final sodium concentration for the category. In other words, we used sales volume data to give extra weight to higher-selling foods in a category and to eliminate very low-volume foods from our calculations.[20]

We developed baselines for packaged foods by reviewing label data on sodium content for the individual food products within a category. We focused on foods making up the top 80 percent of sales by volume in each category. Using both label and sales data for packaged foods, we calculated a sales-weighted average sodium concentration for the category; products with higher sales volume counted for more in the final average.

We developed baselines for commercially prepared foods by reviewing public menu data for the largest national and regional restaurant chains, capturing only those menu items with added sodium. Because sales data on individual products within each restaurant chain were not available, we calculated a sales-weighted average sodium concentration for each category using the total sales of each chain as a proxy value; products from a chain with greater total sales of all products counted for more in the final average. Because sodium concentrations are not always similar in packaged and restaurant versions of a food, we developed two separate baselines for packaged and restaurant (prepared) foods.[21]

C: Target Mean and Upper Bound Sodium Concentrations

For our draft guidance, we developed a model of sodium intake based on our food categories and the 2009-2010 What We Eat in America (WWEIA) survey[22] consumption data (Ref. 5). We estimated that a reduction in mean population intake to near 3,000 mg/day could be attainable if the food industry achieved the short-term goals presented in the draft guidance.

We recognize that any potential changes in the sodium content of the food supply will take time. Table 1 identifies our 2.5-year goals for sodium concentrations in the food supply, both for the

[20] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for a detailed discussion of our use of sales volume data to give extra weight to higher-selling foods and eliminate low-volume selling foods from our calculations.

[21] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for more detail about the development of baseline sodium concentrations.

[22] The National Health and Nutrition Examination Survey is a program of studies designed to assess the health and nutritional status of adults and children in the United States. It is a major program of the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention (CDC). More information about NHANES can be found at http://www.cdc.gov/nchs/nhanes.htm.

target mean and for the upper bound sodium concentrations (defined in the discussion above and further discussed below).[23]

The 2.5-year goals are intended to balance the need for broad and gradual reductions in sodium and what is publicly known about technical and market constraints on sodium reduction and reformulation. The distribution of sodium concentrations in currently available products in each category was a significant factor in developing these quantitative sodium concentration goals. We developed the goals with a particular emphasis on maintaining concentrations needed for food safety, given the function of salt as a food preservative. These short-term goals are within the range of concentrations found in currently marketed foods and are feasible using existing technical strategies.

We acknowledge that small businesses may not have the same resources as larger companies for reaching these goals. However, we anticipate that these goals would ultimately be within reach for all firms, given time and the spread of innovations in food ingredients and manufacturing methods.

We consider it likely that the amount of a sodium-containing ingredient needed to achieve various technical effects (including flavor) in foods could decrease over time, due to advances in food technology, such as flavor science and food preservation. Changes in consumer taste preferences are also possible, and may be more likely, should reformulation occur. Reformulation strategies are expected to take time to implement; as a result, we expect sustainable reductions in the amount of sodium in the food supply to happen gradually. The reformulation strategies will likely vary; for example, sodium concentrations in processed and packaged foods are not always parallel to the sodium concentrations in comparable foods prepared at restaurants and other retail food establishments. The short-term (2.5-year) goals (which include both the target mean concentrations and upper bound concentrations) reflect this differentiation.

We do not provide detailed guidance on the technical details of reducing sodium in this document, although we reviewed the publicly available scientific literature on potential opportunities and technologies for reducing sodium (Refs. 6-8). Experts from the food industry are well-positioned to innovate by exploring combinations of strategies and technologies that are most appropriate for each food category and each food product reformulation while maintaining food safety. However, we want to make clear that broader public health goals and maintenance of nutritional quality are important considerations in developing sodium reduction or reformulation strategies. For example, sodium reduction that relies on increases in added sugars would not be consistent with the public health goals of this guidance.[24]

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[23] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for further discussion on the target mean and upper bounds.

[24] We also recognize that in reformulating products, firms may need to balance additional public health goals, such as reducing acrylamide formation in certain foods (see FDA's Guidance for Industry: Acrylamide in Foods, March 2016, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-acrylamide-foods).

1. Voluntary Target Mean Sodium Concentrations

Table 1 identifies voluntary target mean sodium concentrations for each food category. The voluntary target mean indicates the desired average sodium concentration in each category, weighted by relative sales volume so that more popular products have a greater influence on the category average. Target assignment was based on a default reduction percentage modified by available category-specific information. The extent of targeted reduction in each food category is influenced by the functions of sodium-containing ingredients in the category, as well as the distribution of sodium concentrations we found in products within that category.[25] These values are FDA's goals for each food category as a whole, not necessarily for individual manufacturers who choose to pursue these goals voluntarily. These mean target concentrations represent the benchmarks that we will use to assess the impact of any voluntary efforts by members of the food industry on the overall composition of the food supply. However, individual members of the food industry choosing to pursue sodium reduction may find it helpful to assess the sales-weighted status of their product portfolio in a particular category with reference to the target mean concentration in order to inform decisions about where to focus their voluntary reformulation efforts.[26]

2. Voluntary Upper Bound Sodium Concentrations

Table 1 also identifies voluntary upper bound sodium concentrations for each food category. The upper bound is a standard that could be applied to every individual product in a category, in contrast to the target means, which apply to average concentrations in a food category. Food industry members can compare any of their products in a category to the upper bound concentration for every product in that category. The upper bound for each category is influenced by the corresponding target mean concentration and the current distribution of sodium concentrations for products in that category.[27] The upper bound sodium concentrations are goals and do not represent maximum allowable levels for sodium.

IV. Appendix

Table 1. Voluntary Sodium Reduction Goals: Target Mean and Upper Bound Concentrations for Sodium in Commercially Processed, Packaged, and Prepared Foods (see attached Excel table)

Table 2. Non-Target Categories

The non-target categories are food categories for which we have not developed goals. Non-target categories include those that either did not contain meaningful amounts of added sodium (i.e., are foods with no sodium or with intrinsic sodium that is not added) or did not contribute

[25] FDA consulted with FSIS staff during the development of the meat and poultry categories and target mean concentrations.
[26] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5).
[27] See FDA's Voluntary Sodium Reduction Goals Supplementary Memorandum to the Draft Guidance (Ref. 5) for more details about the calculation of upper bound concentrations.

meaningfully to overall sodium intake because they were consumed rarely (by all ages and ethnicities) and because they provided little contribution relative to the other food groups.[28] [29]

Table 3. Definition of Terms Used in This Document (for the purposes of this guidance only)

[28] As measured by an analysis of the food sources of sodium intake using 2007-2008 WWEIA/NHANES data.
[29] As assessed by a sensitivity analysis to determine if food categories shifted, looking at percent consumer, per user mean, and per capita mean.

Table 2. Non-Target Categories	
General Food Category	**Category and Product Examples**
Dairy	All milk except buttermilk and dry milk
Dairy	Buttermilk
Dairy	Dry milk
Dairy	Yogurt
Dairy	Ice cream/frozen yogurt
Dairy	Hot Cocoa
Dairy	Ice cream bars/cones/sundaes
Dairy	Whipped topping
Dairy	Cream and cream substitute
Dairy	Sour cream
Dairy	Custards/flans
Dairy	Mousse-type pudding
Dairy	Mascarpone cheese
Dairy	Ricotta cheese
Dairy	Fresh Mozzarella cheese
Dairy	Cheese fondue (packaged food)
Dairy	Cream-based fruit dips
Fats, Oils, and Dressings	Animal fats
Fats, Oils, and Dressings	Natural oils
Fats, Oils, and Dressings	Raw commodities
Fats, Oils, and Dressings	Butter – unsalted
Fats, Oils, and Dressings	Margarine, vegetable oil spreads – unsalted
Fruits, Vegetables, and Legumes	Fruit - raw/fresh
Fruits, Vegetables, and Legumes	Fruit – frozen
Fruits, Vegetables, and Legumes	Fruit filling
Fruits, Vegetables, and Legumes	Fruit – canned
Fruits, Vegetables, and Legumes	Fruit - salads/cocktails
Fruits, Vegetables, and Legumes	Fruit – cooked
Fruits, Vegetables, and Legumes	Fruit – juice
Fruits, Vegetables, and Legumes	Fruit – dried
Fruits, Vegetables, and Legumes	Fruit - misc. (sauces, juice bars, etc.)
Fruits, Vegetables, and Legumes	Coconut products
Fruits, Vegetables, and Legumes	Vegetables - raw and/or no added sodium
Fruits, Vegetables, and Legumes	Boiled/baked/raw potatoes, no toppings
Fruits, Vegetables, and Legumes	Dried beans and dried peas
Fruits, Vegetables, and Legumes	Instant potatoes, unseasoned
Fruits, Vegetables, and Legumes	Dried vegetables
Fruits, Vegetables, and Legumes	Vegetable pastes/purees
Fruits, Vegetables, and Legumes	Peppers, Shelf-Stable
Fruits, Vegetables, and Legumes	Pickled Vegetables, excluding pickled cucumbers (pickles)
Fruits, Vegetables, and Legumes	Fruit – pastes/cubes

Fruits, Vegetables, and Legumes	Tomato – puree
Fruits, Vegetables, and Legumes	Crispy fried onions
Fruits, Vegetables, and Legumes	Grape leaves – stuffed/non-stuffed
Nuts and Seeds	Nuts/seeds, unsalted
Nuts and Seeds	Dessert/sweet seed/nut spreads (almond paste, chocolate hazelnut spread, caramel paste, etc.)
Nuts and Seeds	Miso (soy bean paste)
Soups	Liquid/paste bouillon
Soups	Refrigerated soup bases/starters/mixes
Soups	Wet broth/stocks – concentrate/base/starter
Soups	Frozen soups
Sauces, Gravies, Dips, Condiments, and Seasonings	Seasoned salt and seasoning salt
Sauces, Gravies, Dips, Condiments, and Seasonings	Relish
Sauces, Gravies, Dips, Condiments, and Seasonings	Hummus dip, dry-mix
Cereals	Ready-to-eat cereals, shredded
Cereals	Ready-to-eat cereals, granola
Cereals	Ready-to-eat cereals, muesli
Bakery Products	Pie crust/shells
Bakery Products	Soda bread
Bakery Products	Bread pudding
Bakery Products	Tortillas and wraps, corn
Bakery Products	Brownie dough
Bakery Products	Dry mix brownies and cookies
Bakery Products	Liquid bakery batters
Bakery Products	Graham cracker crumbs
Bakery Products	Wrappers – egg roll/won ton/gyoza/spring roll
Bakery Products	Ice cream bowl/cone
Bakery Products	Other desserts (panna cotta, crème brûlée)
Meat and Poultry (and substitutes)	Organ meat, not cured/smoked
Meat and Poultry (and substitutes)	Organ meat, cured/smoked
Meat and Poultry (and substitutes)	Veal
Meat and Poultry (and substitutes)	Lamb and goat
Meat and Poultry (and substitutes)	Game meat, not cured/smoked
Meat and Poultry (and substitutes)	Game meat, cured/smoked
Meat and Poultry (and substitutes)	Prosciutto
Meat and Poultry (and substitutes)	Ground meat/poultry, raw patties
Meat and Poultry (and substitutes)	Pâté/Meat Spreads
Meat and Poultry (and substitutes)	Vegetarian Pâté/ & Terrines
Fish and Other Seafood	Fresh/raw fish and seafood
Fish and Other Seafood	Salted/pickled/dried/smoked fish and other seafood
Fish and Other Seafood	Escargot
Fish and Other Seafood	Seafood pastes/pates

Fish and Other Seafood	Caviar
Eggs and Egg-based Dishes (and substitutes)	Eggs and egg substitutes, no additions during preparation (packaged)
Snacks	Popcorn kernels
Snacks	Sweet popcorn (kettlecorn, caramel, chocolate covered, etc.)
Snacks	Roasted vegetable snacks – corn nuts/wasabi peas, etc.
Snacks	Wheat nuts
Mixed Ingredient Dishes	Sushi
Toddler/Baby Foods	Toddler/baby meat sticks
Confectionary (Sweets)	Sugar and sugar substitutes
Confectionary (Sweets)	Syrups
Confectionary (Sweets)	Gelatin desserts, jellies, jams
Confectionary (Sweets)	Chewing gum
Confectionary (Sweets)	Fudges
Confectionary (Sweets)	Candy and chocolate with nuts
Confectionary (Sweets)	Candy and chocolate without nuts
Confectionary (Sweets)	Non-dairy based bakery desserts
Confectionary (Sweets)	Non-dairy frozen/prepared desserts
Confectionary (Sweets)	Frosting
Confectionary (Sweets)	Chocolate syrup
Confectionary (Sweets)	Chocolate fondue
Confectionary (Sweets)	Chocolate-covered potato chips
Confectionary (Sweets)	Halva
Confectionary (Sweets)	Brittles
Other Foods	Infant food products, infant formula
Other Foods	Meal replacement powders, and supplements
Other Foods	Pasta – shelf-stable
Other Foods	Matzo balls, in broth
Beverages	Non-alcoholic
Beverages	Alcoholic
Beverages	Water

Table 3. Definition of Terms Used in This Document (for the purposes of this guidance only)	
Term	**Definition in this Guidance**
As prepared	Sodium concentration of the product after the food product is prepared according to the product's specific preparation and cooking directions provided on the product label.
Baseline level	The amount of sodium in a category representing the 2010 U.S. food supply. The levels are provided as sales-weighted mean concentrations (sodium in mg per 100 g). Baseline levels were calculated using product nutrition information from commercially available databases and public websites. Scanner data was used for sales weighting packaged foods and restaurant total dollar amounts were used for weighting items at major restaurant chains.
Food Category	A grouping of food products at the level for which a sodium reduction target is suggested. Unless otherwise noted, each category includes all relevant food items containing added sodium. The category product inclusions are not confined to a specific industry sectors (e.g., packaged foods, prepared foods) or point of purchase.
Food Service establishment	An operation that stores, prepares, packages, serves, and sells food directly to the consumer.
Food Group	High level food category grouping for the list of sodium reduction targets (e.g., Dairy; Fats, Oils, and Dressings; etc.).
Goals or "Sodium Reduction Goals"	Refers to both target mean and upper bound concentrations that have been established for 2.5 years after final publication of this guidance.
Hypertension	Hypertension, or high blood pressure, generally means a systolic blood pressure of greater than 140 millimeters of mercury (mm Hg) or a diastolic blood pressure of greater than 90 mm Hg.
Ready-to-eat food	Packaged or prepared food that is ready for human consumption at time of purchase. Ready-to-eat food does not require further addition of ingredients, preparation, or cooking by the consumer to achieve food safety.
Sales-weighted mean	A measurement of sodium content calculated by weighting individual products by volume sales given as the average sodium content in milligrams per 100 grams. A sales-weighted mean gives more weight to items that sell more, thereby providing a preferred monitoring metric for evaluating future sodium reduction progress.
Sodium	Sodium is specified here as the chemical entity or electrolyte "sodium" and is distinguished from sodium chloride, or salt, which is 39 percent sodium by weight (21 CFR 101.74). Examples of other sodium-containing ingredients found in foods include sodium propionate, sodium lactate, and sodium benzoate.

Table 3. Definition of Terms Used in This Document (for the purposes of this guidance only)	
Term	**Definition in this Guidance**
Seasoned (and seasoning)	Addition of salt, herbs and spices to food for the purpose of flavor enhancement.
Target (mean)	The goal sodium level for the category, calculated as the sales-weighted mean sodium level (in milligrams per 100 grams of food).
Upper bound	The goal upper bound sodium content of an individual food product or menu item included in a food category (in milligrams per 100 grams of food).

[ii] This is based on the definition of "food establishment" in FDA's Food Code (2013). http://www.fda.gov/food/guidanceregulation/retailfoodprotection/foodcode/ucm374275.htm

V. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction or are not publications. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff or, in the case of non-publication references, at any website listed. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

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