Bisphenol A
Handling/Processing

Identification of Petitioned Substance

Chemical Names:
2,2-bis-(p-hydroxyphenyl)-2-propane
4,4'-isopropylidene-2-diphenol
4,4'-(1-methylethylidene) bisphenol
4,4'-dihydroxydiphenyldimethylmethane
bis(4-hydroxyphenyl)propane

Other Names:
none

Trade Names:
none

CAS Numbers:
80-05-7

Other Codes:
EC Number 201-245-8
ISCS Number 0634

Summary of Petitioned Use

Bisphenol A (BPA) is currently used as a packaging material for organic products. Like other packaging materials, it is not included on the National List. A technical report on BPA was requested by the National Organic Standards Board (NOSB) Handling Subcommittee in response to a National Organic Program (NOP) memo to the NOSB on this topic[1]. This technical report on Bisphenol A addresses the National List Evaluation Questions applicable to materials in handling. This technical report also addresses specific focus areas requested by the NOSB Handling Subcommittee:

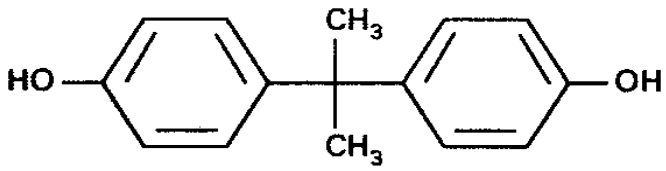
- The report should also evaluate whether Bisphenol A meets criteria of 7 CFR Part 205.272, with special attention to section 205.272(b)(2). *(see OFPA/ USDA Final Rule section)*
- There is much criticism by both sides of the Bisphenol A (BPA) safety debate over the validity of various research methods, from what breed of rats are used to human cell studies in vitro vs. animal studies. There are also alleged collusion, conflict of interest, and bias contentions in some research efforts. Please examine the arguments of both sides objectively using the citations provided and others, and give an evaluation of which research is the most valid. *(see Evaluation Question 10)*
- Evaluate the conclusion from the paper by Yang cited in the NOP memo, that alternative existing compounds, additives, or processing agents that have no detectable estrogenic activity and have similar costs can be identified. Specify what these alternatives are. *(see Evaluation Question 11)*
- Review recent research on some of the BPA alternatives in use, such as Tritan (containing triphenyl phosphate or TPP), Bisphenol S (BPS) and Bisphenol F (BPF) and any others, and evaluate whether they might be better alternatives than BPA in terms of their impact on human health or the environment. *(see Evaluation Question 11)*
- What is the status of BPA in other countries? How widespread are bans on BPA and are any of the alternatives banned as well? What evidence was used in making those determinations? *(see International section)*

Characterization of Petitioned Substance

Composition of the Substance:

Bisphenol A is composed entirely of carbon, hydrogen and oxygen. Its empirical formula is $C_{15}H_{16}O_2$ and its molecular weight is 228.28. It is characterized by two phenol groups and two methyl groups attached to a central carbon as shown in Figure 1 below (Willhite et al. 2008).

[1] https://www.ams.usda.gov/sites/default/files/media/NOSB%20Memo%20Packaging%20Substances%20used%20in%20organic%20food.pdf



Bisphenol A (BPA)

Figure 1: Chemical structure of BPA (Willhite et al. 2008)

Source or Origin of the Substance:

Bisphenol A is a synthetic material produced by the condensation reaction between phenol and acetone. Phenol and acetone are obtained from the Hock process. Benzene and propylene are catalytically reacted to make cumene, which is then oxidized. The cumene hydroperoxide produced is hydrolyzed to phenol and acetone. Benzene and propylene are obtained from distillation of crude oil (Fiege et al. 2000; Weber et al. 2004). Additional information is provided in Evaluation Question 1.

Properties of the Substance:

Bisphenol A is a white solid at room temperature with a mild phenolic odor. Its melting point is 153°C. Further heating causes decomposition at 220°C. It has low volatility, and its vapor pressure is 3.91×10^{-7} mm Hg at 25°C. Density is 1.1-1.2 g/cm^3. It is a very weak acid, and the pKa is 9.59 to 11.30. It has low solubility in water, and its water solubility is 120-300 mg/liter at 25°C. It is more soluble in alkaline solutions and in organic solvents such as ethanol and acetone. More BPA dissolves in octanol than in water, and the octanol/water partition coefficient (log Kow) is 3.34 at 25°C. Log Kow for sea water is 3.52. Its empirical formula is $C_{15}H_{16}O_2$ and its molecular weight is 228.28 (Willhite et al. 2008; Borrirukwisitsak et al. 2012).

Specific Uses of the Substance:

Over 8 billion pounds of BPA are produced worldwide each year. BPA is used to make polycarbonate plastic, and it is a component of epoxy resin. Epoxy resins are used in numerous consumer products, including liners for food and beverage metallic cans. Polycarbonate plastics are used in reusable water bottles, baby bottles, and reusable food containers (Vandenberg et al. 2010). About 75% of canned goods sold in the U.S. are lined with a BPA-based epoxy resin (Geller and Lunder 2015).

Approved Legal Uses of the Substance:

The FDA permits BPA use in canned food and consumer products. The FDA amended food additive regulations to no longer provide for the use of polycarbonate resins in baby bottles and sippy cups as of July 17, 2012. The change was in response to a petition by the American Chemistry Council declaring that this use had been abandoned by manufacturers (USFDA 2012b). The FDA also amended food additive regulations to no longer provide for the use of BPA-based epoxy resins as coatings in infant formula packaging on July 12, 2013. This was in response to a petition from Congressman Edmund Markey claiming that this use has been abandoned (USFDA 2013).

Consumers Union reports that eleven states have banned BPA in baby bottles and sippy cups: California, Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New York, Washington, Wisconsin and Vermont (Consumers Union 2014).

In California, BPA was listed May 11, 2015 as a reproductive toxicant (California 2017a). Currently, the State maintains a list of products containing BPA on the Proposition 65 website (California 2017b). By the end of 2017, organic and other products in food or beverage cans containing BPA will be required to display a warning label declaring that they contain BPA, "a chemical known by the State of California to cause harm to the female reproductive system" (Geueke 2016; California 2017ab).

Action of the Substance:
When used as an inner lining of metallic cans, BPA-based epoxy resins function as preventative coatings to protect the metallic containers from rust and corrosion (Geueke 2016).

Combinations of the Substance:
BPA is a monomer that is polymerized to make epoxy resins and polycarbonate plastics. It is not a precursor to, a component of, or commonly used in combination with a substance(s) identified on the National List.

Status

Historic Use:
BPA was first synthesized by Russian chemist Alexander Dianin in 1891. It was patented in 1917, and manufactured on an industrial scale beginning in 1923 (Neagu 1998). Commercial production of epoxy resins and hard plastics (polycarbonate plastic) using BPA began in the 1950s (Vogel, 2009). U.S. production in the 1980s reached 1 billion pounds, and now over 8 billion pounds of BPA are produced worldwide each year (Vandenberg et al. 2010).

Organic Foods Production Act, USDA Final Rule:

NOSB History
In October 2014, the subject of "Alternatives to Bisphenol A (BPA)" was formally recommended by the NOSB as a research priority (USDA NOSB 2014a). On November 19, 2014, Miles McEvoy, Deputy Administrator of the National Organic Program, wrote a Memorandum to the NOSB stating, "The NOP would like the NOSB to provide recommendations on the use of Bisphenol A (BPA) and similar substances in the packaging of organic food. The NOSB Handling Subcommittee has submitted a request to review the use of Bisphenol A (BPA) in packaging of organic food" (USDA NOSB 2014b). On January 3, 2017, the Handling Subcommittee of the NOSB agreed that the goal was to produce a BPA discussion document for spring 2017 and a proposal for fall 2017 (USDA NOSB 2017a). The Handling Subcommittee produced a BPA discussion document, and it was on the agenda for the NOSB meeting April 19-21, 2017 in Denver, CO (USDA NOSB 2017b).

NOP Regulations relevant to Bisphenol A
The NOP regulations at §205.272 include the following provisions regarding commingling and contact with prohibited substances:

> §205.272 Commingling and contact with prohibited substance prevention practice standard.
> (a) The handler of an organic handling operation must implement measures necessary to prevent the commingling of organic and nonorganic products and protect organic products from contact with prohibited substances.
> (b) The following are prohibited for use in the handling of any organically produced agricultural product or ingredient labeled in accordance with subpart D of this part:
> (1) Packaging materials, and storage containers, or bins that contain a synthetic fungicide, preservative, or fumigant;
> (2) The use or reuse of any bag or container that has been in contact with any substance in such a manner as to compromise the organic integrity of any organically produced product or ingredient placed in those containers, unless such reusable bag or container has been thoroughly cleaned and poses no risk of contact of the organically produced product or ingredient with the substances used.

Concern has been raised (*see NOSB history, above*) regarding the potential for BPA-based packaging to compromise the organic integrity of packaged organic foods, and thereby violate the provisions of §205.272. BPA can leach from epoxy resin can liners or from polycarbonate plastic containers into food and beverages, and high temperatures or the presence of highly acidic or basic solutions increase the amount of leaching (Vandenberg et al. 2010).

Vandenberg et al. (2007) reported 10 studies showing that BPA leaches from plastic linings of metal cans. Each can leached BPA at a range of 4-23 micrograms (μg). (A μg is one-millionth of a gram.) Noonan et al. (2011) tested 78 canned food samples and two frozen food products with liquid chromatography and tandem mass spectroscopy. BPA was detected in 71 of 78 canned food samples in concentrations ranging from 2.6 to 730 nanograms per milliliter (ng/ml). (A nanogram is one-billionth of a gram.) Canned fruits and tuna showed the lowest concentration. The experiment also showed that BPA partitions into the solid part of the food and the canned liquid, and that BPA measurements depend on whether liquid not typically consumed is included in the measurement. Cao et al. (2008) analyzed 21 samples of canned liquid infant formulas for BPA. BPA was present in all samples in amounts ranging from 2.27 ng/g to 10.2 ng/g. BPA has been detected in cans of vegetables, fish and meat, dairy products and infant formula. It also migrates into food from polycarbonate products such as baby bottles, reusable bottles and tableware (Kang et al. 2003).

International

Canadian General Standards Board Permitted Substances List (CAN/CGSB-32.311-2015)
Bisphenol A is not included on the Permitted Substances List. No other food packaging ingredients are identified on the Permitted Substances List, but some sanitizers, cleaners and disinfectants are permitted on organic product contact surfaces, and wax is permitted to coat cheese (Canada 2015). Section 8.1.6 of the General Principles and Management Standards (CAN/CGSB-32.310-2015) requires that organic product packaging maintains organic product quality and integrity, and that packaging materials that minimize harm to the environment throughout their life cycles are preferred.

CODEX Alimentarius Commission, Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (GL 32-1999)
Bisphenol A is not mentioned in the *Codex Alimentarius*. Specifically it is not listed in Annex 2 "Permitted Substances for the Production of Organic Foods." It is also not listed in Table 3 "Ingredients of Non-Agricultural Origin…" or in Table 4 "Processing Aids Which May be Used for the Preparation of Products of Agricultural Origin" (Codex 2001). No other food packaging ingredients are listed, but Annex 1, Section C, part 87 states that "packaging materials should preferably be chosen from bio-degradable, recycled, or recyclable sources," and part 88 states that "organic materials must be protected at all times from contact with materials and substances not permitted in organic farming and handling."

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008
Bisphenol A is not mentioned in EC No. 834/2007. However, in Article 7, "Specific Principles Applicable to the Processing of Organic Food," part b states as a principle, "the restriction of the use of food additives, of nonorganic ingredients with mainly technological and sensory functions and of micronutrients and processing aids, so that they are used to a minimum extent and only in case of essential technological need or for particular nutritional purposes" (EU ECC 2007). No other food packaging ingredients are listed.

Bisphenol A is not mentioned in EC No. 889/2008. Specifically, it is not mentioned in Annex 8, "Certain Products and Substances Which May be Used in Production of Processed Organic Food" (EU ECC 2008). No other food packaging ingredients are listed, but Article 26, Section 4(a) states that operators shall "take precautionary measures to avoid the risk of contamination by unauthorized substances or products."

Japanese Agricultural Standard (JAS) for Organic Production
Bisphenol A is not mentioned in the Japanese Agricultural Standard for Organic Production (JAS 2005). Other food packaging ingredients are not mentioned.

IFOAM - Organics International

Bisphenol A is not listed in the IFOAM Norms for Organic Production and Processing. Specifically, it is not listed in Appendix 4, Table 1: List of Approved Additives and Processing/Postharvest Handling Aids (IFOAM 2012). Other food packaging ingredients are mentioned. On page 61 the document states that, "polyvinyl chloride and aluminum should be avoided," and "operators should not use packaging that may contaminate organic products."

International Bans and Restrictions on BPA

Australia and New Zealand

Food Standards Australia New Zealand concluded that "levels of intake of BPA and plasticizers are very low and do not pose a risk to infant health." Nevertheless, in 2010 the Australian Government started working with retailers on a voluntary phase out of polycarbonate baby bottles (Hengstler et al. 2011).

Canada

In 2010, Canada's Department of the Environment declared BPA to be a toxic substance and added it to Schedule 1 of the Canadian Environmental Protection Act of 1999 (Canada 2017). Advertisement, sale and import of polycarbonate baby bottles were prohibited on March 11, 2010. A Tolerable Daily Intake (TDI) of 25 µg per kilogram of body weight per day (/kg bw/day) was set by Health Canada (Hengstler et al. 2011). Health Canada affirmed the safety of BPA in 2014, but recommended "limiting BPA exposure from food packaging applications to infants and newborns, specifically from pre-packaged infant formula products as a sole source food, for this sensitive segment of the population" (Canada 2014).

Denmark

The Danish government invoked the Precautionary Principle on March 22, 2010, and banned "BPA in materials in contact with food for children aged 0-3 years (infant feeding bottles, feeding cups, and packaging for baby food)" (Hengstler et al. 2011).

European Union

On April 1, 2011, the European Union amended regulation (EU) No. 10/2011 to restrict the use of BPA in plastic baby bottles. BPA is not to be used for the manufacture of polycarbonate infant feeding bottles (EU 2011). On December 12, 2016, the European Union amended Annex XVII to Regulation (EC) No. 1907/2006 by adding "BPA shall not be placed on the market in thermal paper in a concentration equal to or greater than 0.02% by weight after 2 January 2020." The change was in response to a petition from France. France based its hazard assessment on potential adverse effects to the female reproductive system, brain and behavior, obesity, and effects on the mammary gland. A provision was made to monitor Bisphenol S in thermal paper (EU 2016).

France

France banned baby bottles containing BPA on July 2, 2010 (Hengsler et al. 2011). In December of 2012 France passed a law suspending the production, trade and marketing of food containers containing BPA. The ban on containers for infant food was effective on January 1, 2013. On January 1, 2015, the ban took effect for all other food containers (USDA 2013).

Japan

There are no restrictions on BPA in Japan, but between 1998 and 2003 the canning industry voluntarily replaced BPA can liners with polyethyleneterephthalate (PET) (Hengstler et al. 2011).

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 substance. Further, describe any chemical change that may occur during manufacture or

formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

BPA is synthesized through a condensation reaction between phenol and acetone, as shown in Figure 2. The phenol-acetone reaction is spontaneous at room temperature. Two moles of phenol are mixed with one mole of acetone in the presence of concentrated hydrochloric acid or 70% sulfuric acid. A complex mixture is produced, containing mostly BPA along with other phenolic substances (Neagu 1998; Fiege et al. 2000).

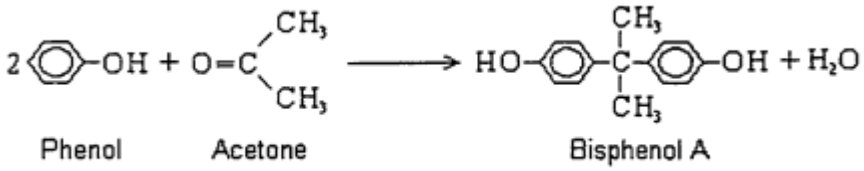


Figure 2: Process for producing BPA (Neagu 1998)

Industrial manufacture uses an acidic catalyst such as gaseous hydrochloric acid (HCl) or sulfonated polystyrene resin. The resin-catalyzed process is preferred for manufacturing. BPA yields with the catalyst Amberlyst-15 can be nearly 90% (Neagu 1998; Fiege et al. 2000).

Industrial processes use phenol mixed with acetone as the feedstock. Alternatively, the feedstock can be a complex mixture of products from the decomposition of cumene hydroperoxide, although this feedstock leads to more impurities and the reaction product is more difficult to purify. In practice, the reaction is run in a solvent such as methylene chloride or acetic acid with excess phenol to prevent self-condensation of acetone (Neagu 1998; Fiege et al. 2000).

If gaseous HCl is used as a catalyst, acetone and phenol are saturated with HCl gas in a reactor at 50°C, and the reaction is stirred for several hours. The HCl is removed and recycled, and water is removed. The crude reaction product is purified by vacuum distillation. Alternatively, it is extracted with a solvent, followed by distillation. For extra purity, the BPA is recrystallized (Neagu 1998; Feige et al. 2000).

Manufacturing of each starting material

The starting materials are phenol and acetone. Most of the industrial phenol and acetone production occurs through the cumene process (Hock process) using benzene and propylene. Benzene and propylene are made from the distillation of crude oil. The benzene and propylene are compressed at 30 atm at 250°C in the presence of aluminum chloride or phosphoric acid (Weber et al. 2004).

Cumene is then isolated and oxidized with oxygen, producing cumene hydroperoxide. Oxidation is either under pressure at 90-100°C, or at atmospheric pressure at 100°C. Cumene hydroperoxide is then hydrolyzed in an acidic medium to produce phenol and acetone. Phenol and acetone can be produced in numerous other ways (Weber et al. 2004).

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

BPA is manufactured using a synthetic chemical process. It is not produced by any naturally occurring biological processes. It is not obtained from an agricultural source (Fiege et al. 2000).

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

BPA is a synthetic substance. There are no natural sources of BPA (Fiege et al. 2000).

Evaluation Question #4: Specify whether the petitioned substance is categorized as generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices (7 CFR § 205.600 (b)(5)). If not categorized as GRAS, describe the regulatory status.

BPA is on the FDA list of approved indirect additives used on food contact surfaces (USFDA 2011a). Although BPA is cited as being classified as GRAS in 1976 (Vogel 2009), BPA is not currently listed as GRAS in Title 21 Part 182, 184 or 186, the SCOGS database, or in the GRAS Notice Inventory.

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

BPA is not a food preservative.

Evaluation Question #6: Describe whether the petitioned substance 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 substance recreates or improves any of these food/feed characteristics (7 CFR § 205.600 (b)(4)).

BPA is not used to recreate or improve flavors, colors, textures or nutritive values lost in processing.

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

Bisphenol A has no effect on the nutritional quality of food, although it may migrate into the food (*see OFPA section for information about BPA leaching into food*) which may have adverse effects on human health *(see Question 10)*.

Evaluation Question #8: 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 substance (7 CFR § 205.600 (b)(5)).

No publications on heavy metal contaminants in BPA are found in the literature. Heavy metals have not been reported as contaminants in the synthesis and production of BPA (Fiege et al. 2000; Neagu 1998).

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)).

Sewage contains the BPA eliminated by humans who have been exposed to BPA. Sewage may also contain BPA released in wastewater of factories that produce it. Water treatment plants can remove 37-94% of the BPA present, and the rest is released into surface water (Crain et al. 2007).

Most surface water concentrations of BPA in the United States are below 0.1 µg/liter, but concentrations up to 12 µg/liter have been found. BPA is degraded by microbes in river water with an aerobic half-life of about 4.5 days. Very little BPA degrades under anaerobic conditions (Crain et al. 2007).

Discarded polycarbonate plastics are another source of BPA in water. Polycarbonate plastics sink in water and end up on stream bottoms. BPA is adsorbed by soil and sediments. The soil adsorption coefficient (*K*oc) of BPA ranges from 314 to 1524. This relatively high value means that BPA can accumulate in sediments. Sediment concentrations (11 µg/liter) can be nearly 200 times water concentrations (0.058 µg/liter) (Crain et al. 2007; Kang et al. 2006).

BPA leaches into the environment from plastics in landfills. Landfill leachate levels can range from 1.3 ng/ml to 17.2 µg/ml (ppm), averaging 269 ng/ml (ppb). Water sources near landfills often have the highest BPA concentrations (Crain et al. 2007). BPA in septic tanks may leach out into groundwater and contaminate wells. BPA has been found in drinking water wells at levels up to 32.9 µg/liter (Rudel et al. 1998).

Bioaccumulation and Toxicity to Aquatic Organisms and other Animals

Fish swimming in BPA contaminated water moderately bioaccumulate BPA. When surface water levels range from <0.01 to 0.33 ng/ml, BPA levels in fish vary from 2 to 75 ng/g dry weight (DW) in the liver, and from 1 to 11 ng/g DW in the muscle. BPA has been found in fish at supermarkets at levels from 13.3 ng/g to 213.1 ng/g wet weight. Concentrations of 15 µg/kg have been measured in fish in Japan (Kang et al. 2006).

BPA has an acute toxicity in the range of about 1–10 µg/ml for a number of freshwater and marine species. Reproduction of the waterflea, *Ceriodaphnia dubia*, is reduced upon exposure to 1 µg/ml (Kang et al. 2006). Concentrations of 200 µg/liter to 5 mg/liter can produce birth defects in amphibians (Crain et al. 2007). Exposure of *Xenopus laevis* to 22.8 µg/liter feminized them. About 200 ppm can cause abnormalities in female quail, *Coturnix japonica*. Alligator eggs, *Caiman latirostris*, produce all females when exposed to 140 ppm BPA (Crain et al. 2007).

Significant concentrations of BPA have the potential to alter testicular structure and function in fishes. When the fat head minnow, *Pimephales promelas*, was exposed to 16 µg/liter of BPA, it had reduced numbers of mature sperm. Brown trout, *Salmo trutta*, exposed to environmentally relevant 1.75 to 5 µg/ml of BPA had reduced sperm density and motility. Ramshorn snails, *Marisa cornuarietris*, have enhanced egg production when exposed to BPA levels of 13.9 ng/liter, a significant concentration (Crain et al. 2007).

Zebrafish, *Danio rerio*, exposed to 0.0068 µMolar concentrations showed a 180% increase in neural development in the hypothalamus. This is an area of the brain associated with hyperactivity. This concentration is 1,000 times lower than average human exposure levels (Kinch et al. 2015; Nutt et al. 2015).

Though high levels of BPA can feminize fish, reptiles and birds, environmental exposures do not reach these levels. Environmental concentrations can reduce sperm output in fish and elevate vitellogenin concentrations. Vitellogenin production in males is a marker for estrogen exposure. There may also be other effects, such as altered brain development, that have not been detected (Crain et al. 2007; Kinch et al. 2015).

<u>Evaluation Question #10:</u> 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)).

There is concern about BPA because it has estrogenic activity, is a high volume industrial chemical, and much of the U.S. population is exposed to it (Vogel 2009; Dodds and Lawson 1936; NTP 2008).

Synthetic estrogens are known to cause health problems. In the 1930s, British chemist Charles Dodds was trying to develop a synthetic estrogen. Bisphenol A (BPA) had structural similarities to the natural estrogen estradiol, and Dodds found that BPA had estrogenic activity. Further research led to the potent synthetic estrogen diethylstilbestrol (DES), which is structurally related to BPA. When DES was commercialized, pregnant women who took DES to prevent miscarriages exposed their developing fetuses to it.

Epidemiological studies showed that females exposed in the womb to DES later developed a rare kind of vaginal cancer, and DES was banned in 1971.(Vogel 2009; Dodds and Lawson 1936).

Human Exposure to BPA from Food

Food is the primary source of human exposure to BPA (Kang et al. 2006), although it is also found in water, cigarette filters, house dust, thermal receipt paper and other places (Vandenberg et al. 2007). Christensen et al. (2012) performed a fasting experiment with human volunteers and found that about two-thirds of the BPA exposure was dietary. BPA migration from food containers into the food leads to dietary exposures *(see OFPA Section for information about BPA leaching into food)*.

Adults in the general population have exposures of 0.008-1.5 µg/kg bw/day (NTP 2008). Estimates of exposure from leaching of consumer products are 1-5 µg/kg bw/day (Vandenberg et al. 2007). Another estimate from the European Commission's Scientific Committee on Food was 0.48-1.6 µg/kg bw/day. Higher estimates of exposures at 0.6 to 71.4 µg/kg bw/day were calculated from measurements of urine concentrations (Vandenberg et al. 2007).

Infants and children have the highest exposures other than BPA industry workers. According to a review published by the National Toxicology Program (NTP 2008), some U.S. human exposures to BPA are as follows: formula fed human infants 0-6 months are exposed to 1-11 µg/kg bw/day; when breast fed, exposure is 0.2 to 1 µg/kg bw/day. Infants 6-12 months have exposures of 1.65-13 µg/kg bw/day. A child 1.5-6 years has exposures of 0.43-14.7 µg/kg bw/day. Occupational exposures are the highest at 0.43 to 100 µg/kg/day (NTP 2008). According to Vandenberg et al. (2007), exposure to BPA is high in newborns, at 24 µg/kg bw/day, due to polycarbonate baby bottles. At 3 months, exposure drops to 15µg/kg bw/day because of weight gain. Edginton and Ritter (2009) estimate that newborn exposure to BPA may be 3-10 times higher than adults.

In Europe, estimated daily BPA intake for infants and toddlers is 0.875 µg/kg bw/day. Adult men and women of childbearing age have estimated exposures of 0.388 µg/kg bw/day, and the highest exposure of 1.449 µg/kg bw/day is for adolescents (EFSA 2015). In New Zealand, BPA accounts for 34% of estrogenic exposure in the diet, and estimated intakes are 4.1-4.8 µg/day (Vandenberg et al. 2007).

Estimated human exposure levels given above are greater than levels that have caused adverse reactions in animals (Richter et al. 2007; Vandenberg et al. 2007; vom Saal et al. 2007; Wetherhill et al. 2007; Vandenberg et al. 2010; Calafat et al. 2008). Adverse effects in animals have been seen at doses ranging from 0.025 to 50 µg/kg bw/day. Effects on prostate, breasts and ovaries, early puberty, changes in brain structure and behavior, decline in testosterone, and neurological effects have been seen in animals (NTP 2008; vom Saal and Hughes 2005; Markey et al. 2005; Munoz-de-Toro et al. 2005; Newbold et al. 2009; Honma et al. 2002; Akingbemi et al. 2004; Murray et al. 2007; Ho et al. 2006; Palanza et al. 2002; Kubo et al. 2003; Leranth et al. 2008).

Metabolism of BPA following exposure

When humans are exposed to BPA, it is mostly metabolized by the liver and excreted in the urine. Metabolites are the glucuronide and the sulfate. (In this section, unmetabolized BPA is called "BPA" or "free BPA", and the metabolites are called "metabolites" or are specifically identified by name, while total BPA refers to the metabolites and free BPA collectively.) Both free and metabolized BPA have been found in blood and in urine. Humans excrete BPA metabolites relatively slowly, with a half-life of about 5.4 hours, but some are still present after 30 hours (Dekant and Volkel 2008; Vandenberg et al. 2007; 2010; Corbel et al. 2015). The BPA metabolites are generally thought to be biologically inactive (Snyder et al. 2000; Matthews et al. 2001; Zalko et al. 2003).

Urinary BPA has been detected in 93% of the U.S. population. Most of the BPA present in urine is in the form of the glucuronide or sulfate metabolites, but free BPA has also been found. Average total BPA for men is 1.63 ng/ml, and for women it is 1.12 ng/ml (Calafat et al. 2008). One study administered BPA at 25µg/kg, and after 5 hrs the urine contained 1.14 ng/ml of free BPA and 10.1 ng/ml of glucuronide (Volkel et al. 2005; Vandenberg et al. 2007). When 84 volunteers ate canned soup, total BPA concentrations (free

BPA plus metabolites) in their urine increased 1000% (Carwile et al. 2011). Free BPA has been found in human serum at 0.2 to 20 ng/ml, and the average is about 0.2 ng/ml (Vandenberg et al. 2007). The National Toxicology Program found blood levels in pregnant women ranged from 0.5 to 22.4 ng/ml, with a mean of 5.9 ng/ml (NTP 2008).

Vandenberg et al. (2007 and 2010) reviewed the BPA exposure data and found that the highest BPA levels were found in the placenta. Average free BPA in placenta was 11.2 ng/g, with an upper level of 104.9 ng/g. Free BPA was found to cross the placenta into the fetus. Concentrations of 8.3 ng/ml were measured in amniotic fluid at 15-18 weeks. Measurements of amniotic fluid, maternal and fetal serum and placenta show fetuses could be exposed to 1-3 ng/ml of biologically active BPA. Free BPA in breast milk averaged 0.4 ng/ml, and average total BPA was 1.1 ng/ml. (Vandenberg et al. 2007; Vandenberg et al. 2010; Dekant and Volkel 2008). (*Exposures are discussed further under Human Kinetics below.*)

Regulatory History of BPA

Increased exposure to BPA led to regulatory scrutiny. The 1958 version of the Federal Food, Drug, and Cosmetic Act established regulation of chemical hazards in food. If a substance was determined to be carcinogenic, no amount was allowed. If toxic, but not carcinogenic, the law allowed thresholds to be established below which the chemical was thought to be safe (Vogel 2009).

The National Toxicology Program (NTP) is part of the National Institute of Environmental Health Sciences, which in turn is part of the National Institutes of Health within the U.S. Department of Health and Human Services. The NTP does research on toxins and carcinogens that might cause health problems in the U.S. The NTP published an assessment of BPA carcinogenicity in 1982 and found there was "no convincing evidence" of carcinogenicity (NTP 1982). Since it was not a likely carcinogen, toxic thresholds could be defined, and in 1986 the EPA set the toxic threshold at 50 µg/kg of body weight per day. Exposures below this threshold were considered to be safe. When this was published, the EPA knew that BPA was estrogenic, but because it was metabolized quickly BPA was not thought to be a hazard (Vogel 2009).

BPA can potentially cause problems below the toxic threshold through endocrine disruption (Vogel 2009; Dodds and Lawson 1936). Endocrine disruption by chemicals was first formally recognized and defined at the Wingspread Conference in Wisconsin in 1991. Before then, there was a history of estrogenic chemicals in the environment and in wildlife (Vogel 2009; Colborn et al. 1996; Vandenberg et al. 2014b).

In 1993, Stanford researchers observed that BPA leaching from polycarbonate flasks in their laboratory caused estrogenic effects in breast cancer cells (Krishnan et al. 1993). BPA was tested for estrogenic activity in mice at doses lower than the toxic threshold in 1997. BPA was known to be estrogenic, but the effects were thought to be weak. BPA was a stronger estrogen than expected in these tests, and increased prostate weights were found in the mice that were tested (Vogel 2009; vom Saal et al. 1997; vom Saal et al. 1998; Nagel et al. 1997).

Adverse effects below the toxic threshold prompted NTP to call for a new testing paradigm in 2002 (Melnick et al. 2002). This suggestion was met with controversy. Some researchers, including researchers from the chemical industry, supported a "weight of evidence evaluation." They believed that only experiments involving a large number of animals, a wide distribution of doses, and following Good Laboratory Practices (GLP) should be considered reliable or valid. Also, they advocated that oral doses should be the preferred route of administration, as this most closely represents human dietary exposure (Vogel 2009). More information on the "weight of evidence evaluation" and GLP is provided below.

Good Laboratory Practices

GLP are a set of principles instituted to provide a reliable framework for experiments. Much of GLP is concerned with animal treatment, documentation, and other housekeeping parameters. GLP experiments emphasize large numbers of animals, and testing of several dose levels. GLP experiments are often characterized by classic macroscopic endpoints such as organ damage and tumor formation (Myers 2009ab; Vogel 2009; Tyl 2009).

Regulatory experiments use large numbers of animals, and oral doses are preferred. Oral doses are thought to be more relevant to human exposures of BPA, since exposure is mostly through the diet. However, dermal and inhalation exposure is also likely (Vandenberg et al. 2013bc).

Oral doses are more easily deactivated than injected, dermal, or inhaled doses, and can give lower estimates of harm. Animals have considerable individual variation, so results will vary from animal to animal. Large numbers of animals minimize the effects of individual variation (Tyl 2009).

Weight of the Evidence

If the weight of the evidence evaluation, as mentioned above, is used, a large number of studies can be rejected. This evaluation protocol was followed by a Harvard study funded by the American Plastics Council in 2004 that found BPA to be safe at doses below the toxic threshold. Most emphasis was placed on a couple of industry studies that some have criticized as flawed (Gray et al. 2004; Vom Saal and Hughes 2005; Vogel 2009).

Another study funded by the American Plastics Council and published by the Gradient Corporation in 2006 also found no negative effects from BPA at low doses. Experiments with non-oral doses were rejected for this report, and most weight was given to industry sponsored studies that followed GLP (Goodman et al. 2009; Vogel 2009).

Bias was suspected in these industry studies because, of the 115 studies on BPA that had been completed to this time, those funded by the government (90%) found potential problems with BPA, while 11 industry funded studies (10%) found BPA to be safe (Vom Saal and Hughes 2005; Vogel 2009).

In August of 2008, the FDA released a draft assessment that found BPA to be safe at doses normally encountered. Emphasis was placed on two industry-generated GLP studies, and hundreds of experiments that were not GLP were excluded (USFDA 2008a). An FDA Science Board Subcommittee reviewed this study and disagreed with the exclusion of hundreds of low dose BPA studies (USFDA 2008b; Vogel 2009).

FDA expressed concern about BPA in 2010 (USFDA 2010), and followed with literature reviews in 2011 (USFDA 2011) and in 2012 (USFDA 2012a). On July 12, 2012, the FDA amended food additive regulations to no longer provide for the use of polycarbonate resins in baby bottles and sippy cups. Polycarbonate resins are a source of BPA (USFDA 2012b). Also, FDA amended food additive regulations to no longer provide for the use of BPA based epoxy resins in baby formula packaging on July 12, 2013. This action was in response to a petition by Congressman Edmund Markey claiming that this use had been abandoned by industry (USFDA 2013).

Another literature review was completed by FDA in 2014 (USFDA 2014a), and a Final Report was issued the same year (USDA 2014b). The latest evaluation in 2014 could find no convincing evidence of a human safety problem below the toxic threshold (USFDA 2014b). However, three endpoints were identified as potential hazards: "developmental neurotoxicity related to molecular or neuroanatomical endpoints with varying routes of administration, cardiovascular disease-related factors based on human epidemiology studies, and sperm/testicular/hormone related factors based on very limited supporting animal data" (FDA 2014ab).

In Europe, the European Food Safety Authority (EFSA 2015) made a safety assessment entirely based on probable human exposures and the ADI (Acceptable Daily Intake). The ADI previously had been deduced based on the Lowest Observed Adverse Effect Level (LOAEL) 50 mg/kw bw/day and No Observed Adverse Effect Level (NOAEL) 5 mg/kg bw/day. These gave an ADI or Reference Dose of 50 µg/kg bw/day. Based on the latest information, EFSA (2015) recommended a lower ADI of 4 µg/kg bw/day.

Methodology of FDA Toxic Threshold

The FDA maintains that exposures to BPA below the toxic threshold are safe. The toxic threshold was established using rodent experiments that followed FDA regulatory guidelines and GLP. Classical regulatory testing involves large numbers of rodents, and several different and increasing oral doses. The

dose is increased until an adverse effect is noted. Endpoints measured are organ damage, tumor formation, low birth weights, visible birth defects, and other mostly macroscopic outcomes. Biochemical measurements, such as levels of cholesterol, serum enzymes and others are made if there are known associations to adverse endpoints (Tyl 2009).

Doses are extrapolated to the lowest dose where visible effects occur, the Lowest Observed Adverse Effect Level (LOAEL) or the No Observed Adverse Effect Level (NOAEL). Division of this dose by a safety factor of 100 or 1000 gives the Reference Dose (RfD) or the Acceptable Daily Intake (ADI). Daily doses below the RfD or ADI are presumed to be safe for humans (Tyl 2009; USFDA 2014a; USFDA 2017). The BPA LOAEL for reproductive effects is 50 mg/kg bw/day. The NOAEL for systemic effects is 5 mg/kg bw/day. The RfD is the same as the ADI, 50 µg/kg bw/day (USFDA 2017).

Two Different Testing Paradigms

BPA has become a case in point that reflects the conflict between two very different safety testing paradigms. Classical toxicologists believe that increasing the dose will increase the measured effect over all ranges of concentrations. In other words, they expect that doses and effects follow a monotonic and often linear trend. There is then a lower threshold below which the dose has no effect (Vandenberg et al. 2009).

However, many endocrinologists follow another paradigm. Hormones and endocrine disruptors exert effects at very low doses, and there may be no detectable effect at all at high doses (Vandenberg et al. 2012; Zoeller et al. 2012). Endocrine disruption may not follow a monotonic response. A monotonic response occurs when effects observed increase continuously as the dose administered increases. High doses produce greater effects than low doses. Endocrine disruptors bind to receptors to cause a response, and binding to receptors may not be a monotonic response to concentration. Effects triggered by the receptor may not be a monotonic response of percent binding sites occupied. High doses may not show an effect, but effects might be seen at very low doses (Welshons et al. 2003; Vandenberg et al. 2012; 2014ab).

To determine safety, FDA regulators follow weight of the evidence evaluations. Some experiments are given greater weight than others when a regulatory decision is made. For BPA, regulators rely extensively on a few rodent experiments that follow regulatory guidelines and GLP. They give low weight to tissue culture experiments, epidemiology, and animal experiments that do not meet GLP guidelines. FDA regulators also attach great importance to kinetic experiments that show BPA is quickly metabolized (USFDA 2014a; USFDA 2017; EFSA 2015; Volkel et al. 2002; 2005; 2008).

Adverse Effects at Low Doses

Hundreds of peer reviewed animal experiments, in vitro experiments and epidemiological studies suggest that BPA has adverse health effects in humans at doses below the FDA toxic threshold. BPA could cause problems at low doses because it is an endocrine disruptor and acts like a natural hormone (Vandenberg et al. 2014b).

BPA levels in humans have been associated with an array of human health problems, such as obesity, type 2 diabetes, neurobehavioral problems such as ADHD, increases in prostate and breast cancer, early onset of puberty in girls, male genital abnormalities, cardiovascular disease, hypertension, reduced sperm quality, altered hormone concentrations, and other problems (Rochester 2013). Experiments with animals support the epidemiological results (Richter et al. 2007; Vandenberg et al. 2010).

In a 2008 review, the Center for the Evaluation of Risks to Human Reproduction (CERHR), which is part of the National Toxicology Program, found that "The NTP has some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A," and "the possibility that bisphenol A may alter human development cannot be dismissed" (NTP 2008; Vogel 2009).

A review of the low dose effects of BPA was published by The National Institute of Environmental Health Sciences in 2007 (vom Saal et al. 2007) The review, which was called the Chapel Hill Consensus, found adverse effects in animals at concentrations known to occur in humans. They found that BPA in the tests

was associated with organizational changes in the prostate, breast, testis, mammary glands, body size, brain structure and chemistry, and in the behavior of laboratory animals (Richter et al. 2007, vom Saal et al. 2007; Vogel 2009). The Chapel Hill Consensus and the report from CERHR were both taken very seriously and generated much of the initial concern about exposure to BPA. Later epidemiological studies also generated concern (Lang et al. 2008; Braun et al. 2009; Braun et al. 2011, Rochester 2013).

Possible adverse effects of BPA in humans were established by animal experiments, tissue culture experiments, and by results of epidemiology studies in humans (Wetherill et al. 2007; Crain et al. 2007; Rochester 2013). These studies are further discussed below.

Criteria for Valid and Reliable Animal Experiments

An experiment does not have to follow GLP to be considered valid. Put simply, an experiment is considered valid if it measures what it was intended to measure, and is considered reliable if repetition gives the same results. To be useful, animal experiments should be both valid and reliable. Another requirement of a useful experiment is that the results should be relevant. Sometimes, formal criteria are established to make sure an experiment is useful (Myers et al. 2009a; Richter et al. 2007).

The low dose experiments that showed adverse effects of BPA were reported in peer reviewed publications. To be considered valid, the experiments met a number of criteria. As mentioned above, the Center for the Evaluation of Risks to Human Reproduction (CERHR), which is part of the NTP, found "The NTP has some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A," and "the possibility that bisphenol A may alter human development cannot be dismissed" (NTP 2008; Vogel 2009).

Criteria used by the National Toxicology Program (NTP)

Criteria used by the NTP in evaluating the validity of BPA animal experiments included the use of large enough sample sizes, statistical control for litter effects, and the use of positive controls. Positive controls for BPA are estrogenic compounds such as estradiol that are administered to show the experiment is sensitive enough to find an effect (NTP 2008). Positive controls, use of sensitive species, and care to avoid environmental contamination from food, bedding, and cages were suggested by an earlier NTP review in 2002 (Melnick et al. 2002).

In the NTP review, observations at more than one dose level were given higher weight. Greater weight was given to experiments that established a linkage between an experimental result and an adverse health effect. Oral doses were preferred in mature rodents, but injection experiments were accepted for fetal and neonatal rats. Since fetal and neonatal rats cannot easily metabolize oral doses, blood levels from oral doses and injections are similar (Taylor et al. 2008). Reproducible experiments were emphasized. In instances of difficult interpretation, NTP gave weight to supporting data "at the mechanistic, cellular or tissue level" (NTP 2008).

Criteria used by the Chapel Hill Consensus

The Chapel Hill Consensus found adverse effects in animals at concentrations known to occur in humans. Experiments were considered valid if they met a number of criteria, and many criteria were similar to those used by the NTP. Suggestions included the use of a sensitive animal strain such as the CD-1 mouse, and the use of a positive control. Estradiol was considered the best positive control for injection, and DES or ethinylestradiol for oral administration. Animal feed should be exactly specified, and drinking water and cages should be verified free of BPA. The exact method of dosing should be specified. Standard animal handling procedures had to be followed (Richter et al. 2007). These criteria and those of Vom Saal and Welshons (2006) and Welshons et al. (2006) are used below to evaluate the GLP experiments used by the FDA.

Criticism of GLP Low Dose Studies

An experiment following GLP can still be considered flawed. Problems can be identified using the criteria developed by the National Toxicology Program and the Chapel Hill Consensus.

Cagen et al. (1999) and Ashby et al. (1999) used diethylstilbestrol (DES) as the positive control but were not able to detect any effect of DES. According to the NTP criteria described above, these experiments have no validity due to lack of sensitivity. Ema et al. (2001) and Tyl et al. (2002) used the Charles River, Sprague Dawley (CD-SD) rat, which has low sensitivity to estrogens such as ethinylestradiol. According to NTP criteria, these experiments should be rejected (Myers et al. 2009a; vom Saal and Hughes 2005; Welshons et al. 2006; Vandenberg 2014b).

Tyl et al. (2008ab) used the CD-1 mouse, which should have been sensitive to low doses of the estradiol positive control. But the mice in these experiments were relatively insensitive to estradiol. According to the NTP criteria, Tyl 2008ab did not have a sensitive enough assay system. One possibility might have been that the rat chow contained phytoestrogens that interfered with the assay (Myers et al. 2009a; NTP 2008).

Another criticism of Tyl et al. 2008ab is that the endpoints that were measured were not relevant to the BPA literature. "Although findings regarding brain structure, brain chemistry, and behavior represent the largest portion of the literature on low-dose BPA, Tyl et al. (2008a) did not examine any neurobehavioral endpoints" (Myers et al. 2009a). Tyl et al. (2008ab) measured macroscopic tissue endpoints such as "wet weight changes of tissues, gross histologic changes, and developmental landmarks such as vaginal opening" (Myers et al. 2009a). However, many of the low dose BPA endpoints are not macroscopic (Myers et al. 2009a).

Response to Criticism

As mentioned above, major criticisms of the aforementioned GLP low dose studies were no positive controls (Tyl et al. 2002), large doses of positive controls needed to produce an effect (Tyl 2008ab), use of insensitive species (Tyl et al. 2002), no measurement of neurobehavioral endpoints (Tyl et al. 2008a), and use of outdated techniques (Tyl et al. 2008ab). Tyl (2009) responded that "a positive control group is neither required nor routinely employed in guideline-compliant studies." Large doses of estradiol (Tyl et al. 2008ab) needed to produce an effect were explained by difficulty with oral dosing. The lack of neurobehavioral endpoints was explained by stating that "guideline compliant studies must use appropriate routes and validated endpoints to detect adverse outcomes, for example, changes in survival, growth and/or development, body and/or organ weights, histopathology, and systemic and reproductive organ function." Response to the use of outdated techniques was "risk relevant guidelines…do not include unvalidated, cutting edge techniques because they are required to use validated endpoints and parameters…" (Tyl 2009).

Later GLP experiments accepted as valid by the FDA were Delclos et al. (2014) and Churchwell et al. (2014). Delclos et al. (2014) used the NCTR Sprague Dawley rat, which should have been sensitive to BPA, and they used positive estrogenic controls (ethinyl estradiol), and made a good faith effort to exclude environmental sources of BPA. They had both naïve controls and those for the dose solvent (vehicle). Nevertheless, "BPA glucuronide was detected in the serum of vehicle and naïve control animals at levels similar those detected in treated animals dosed with 2.5 μg BPA/kg bw/day." These results were established by Churchwell et al. (2014) who did quality control for the experiment. Since controls were exposed to BPA at the same levels as treated animals at low doses, meaningful conclusions about low dose effects cannot be made (Hunt et al. 2014). A lack of meaningful conclusions may indicate that the experiment is flawed. Differences between controls and the treated group would not be detectable (Hunt et al. 2014).

High Dose Animal Experiments

The literature agrees that BPA can be toxic at high doses. Doses of 500 mg/kg bw/day in rats or 875 mg/kg bw/day in mice lead to fetal death, decreased litter size, and decreased numbers of live pups per litter. Doses of 300 mg/kg bw/day in rats lead to reduced growth. Doses of 50 mg/kg bw/day in male and female rats lead to delayed puberty (NTP 2008).

Low Dose Animal Experiments

Animal experiments can provide a good estimate of effects. Also, animal experiments possess a profile that includes detoxification and elimination. Weaknesses are that animals are not perfect models of humans.

For instance, in the case of BPA, humans convert it to a glucuronide and eliminate it in urine. Rats eliminate the glucuronide produced in feces (NTP 2008).

More than 275 animal experiments with well-characterized, valid criteria have registered the effects of BPA doses below the FDA LOAEL of 50 mg/kg bw/day (Vandenberg et al. 2013c). More than 90% of these studies suggest that BPA causes harm (Vom Saal and Hughes 2005). "A large number of these studies include doses below the US EPA reference dose of 50 µg/kg/day and demonstrate effects even in this low dose range" (Vandenberg et al. 2013c). These experiments found changes in liver enzymes, insulin regulation, development processes and behavior, mammary gland changes, effects on ovaries and other effects (Richter et al. 2007; Vandenberg et al. 2012; Vandenberg 2013a).

Adverse effects in animals have been seen at very low doses ranging from 0.025 to 50 µg/kg bw/day (*see Human Exposure above*). Effects on prostate, breasts and ovaries, early puberty, changes in brain structure and behavior, decline in testosterone, and neurological effects were seen. Humans can be exposed to BPA at these levels. But several of these animal experiments used non-oral doses, and therefore are excluded from regulatory evaluations (NTP 2008; vom Saal and Hughes 2005; Tyl 2009).

Tissue Culture Experiments

Tissue cultures allow direct assessments of molecular parameters such as receptor binding and gene expression. However, interpretation of results in terms of whole organisms is sometimes difficult because tissue culture experiments always give worst case results. Tissue cultures are not protected by the biological mechanisms available in the intact animal, such as metabolic inactivation by the liver and cell repair (Wetherill et al. 2007; Tyl 2009).

Molecular and cell culture approaches such as gene transcription and receptor activation predict what might happen to these cells in an intact organism. These approaches are not usually included in a regulatory evaluation because they are not easily associated with an adverse outcome in an intact animal (Tyl 2009).

The regulatory in vivo threshold of 50 µg/kg bw translates to an in vitro BPA concentration of about 10^{-7} molar, or <50 ng/ml (ppb or parts per billion). Tissue culture effects have been noted at concentrations 100,000 times lower, at 10^{-12} molar or 0.23 ppt (parts per trillion) (vom Saal and Hughes 2005).

BPA mimics the effects of estrogen, and BPA binds to estrogen receptors ER(alpha) and ER(beta), with 10X higher affinity for the latter. It is less active than estrogen on nuclear receptors, but it can also bind to membrane receptors, producing "non-genomic steroidal responses" with potency similar to estrogen (Wetherill et al. 2007).

BPA also performs actions at the androgen receptor, and may act as an androgen antagonist. BPA may inhibit aromatase, which converts testosterone to estradiol. In Leydig cells of the testicle, 0.1 nM (nanomolar) BPA can reduce testosterone biosynthesis by 25%. It also binds to estrogen related receptor gamma (ERR-gamma). BPA can bind to the thyroid hormone receptor, and may have effects on thyroid function. It can alter dopamine responses in neural cells (NTP 2008; Wetherill et al. 2007; Vandenberg 2013a).

A "non-classical membrane ER" in pancreas cells is affected by BPA, leading to changes in glucose metabolism. BPA may affect immune cells, modulating immune and inflammatory responses. Wetherill et al. (2007) states, "it is possible that long term exposure to BPA might significantly affect the innate immunity in humans." BPA can affect IL-4, a pro-inflammatory cytokine associated with allergic responses (Wetherill et al. 2007).

Epidemiology

Human epidemiology studies are done by measuring urine or blood concentrations of BPA in humans, and relating the measurements to possible adverse effects. The strength of epidemiology is that results are directly applicable to humans. The weaknesses include small samples, information that may rely on recall

that leads to recall bias, confounding parameters, and general complexity that defies simple interpretation. Epidemiology studies also just establish associations between exposures and adverse effects. They do not prove causation (Rochester 2013).

Rochester (2013) reviewed 91 studies on adverse effects of BPA in humans. Six studies found associations with diabetes, seven showed cardiovascular effects, 10 showed an association with obesity, nine showed neurobehavioral effects, and two studies found an association with asthma. Nine studies found an association between maternal exposure during pregnancy and adverse endpoints measured in offspring. Timing of exposure was critical in three studies, and postnatal exposures led to adverse effects in three studies.

Rochester (2013) found that "recent human studies indicate that BPA exposure in adults may be associated with reduced ovarian response and IVF success, reduced fertilization success and embryo quality, implantation failure, miscarriage, premature delivery, reduced male sexual function, reduced sperm quality, altered sex hormone concentrations, PCOS [polycystic ovary syndrome], altered thyroid hormone concentrations, blunted immune function, type-2 diabetes, cardiovascular disease (i.e., heart disease, hypertension, and cholesterol levels), altered liver function, obesity, albuminuria, oxidative stress and inflammation, and altered epigenetic markers and gene expression." The findings also suggest that "exposure to BPA during gestation could result in increased spontaneous abortion, abnormal gestation time, reduced birth weight, increased male genital abnormalities, and childhood obesity" (Rochester 2013). "Particularly strong are the associations between early BPA exposure and altered behavior and disrupted neurodevelopment in children, as well as increased probability of childhood wheeze and asthma" (Rochester 2013).

Many of these findings from Rochester (2013) had been noted in earlier reviews (NTP 2008; Braun et al. 2011; Lang et al. 2008; Trasande et al. 2012; Spanier et al. 2012). The association between BPA exposure and anxiety, depression, aggression and hyperactivity in children was supported by a later review (Ejaredar et al. 2017). The association with diabetes was also supported in other studies (Sowlat et al. 2016). A later study also showed that BPA could interfere with circulating levels of vitamin D in humans (Johns et al. 2016).

The adverse effects found by Rochester (2013) are also supported by similar adverse findings from in vitro experiments and in vivo animal studies at environmentally relevant doses (Richter et al. 2007; Bonefel-Jorgensen et al. 2007; Moriyama et al. 2002; vom Saal et al. 2007; Fernandez et al. 2010; Signorile et al. 2010; Soto et al. 2008; Miyawaki et al. 2007; Xu et al. 2002; Toyama et al. 2004; Berger et al. 2008; Chitra et al. 2003; Takao et al. 1999; Alonso-Magdalena et al. 2010; Benachour et al. 2009; Rubin et al. 2001; Rubin et al. 2009; Palanza et al. 2008; Masuno et al. 2005).

Human Kinetics

Regulators give weight to kinetic experiments (study of absorption, distribution, metabolism, and excretion of substance) that show that oral doses in humans are quickly deactivated (FDA 2014ab; EFSA 2015; Volkel et al. 2002; 2005). In healthy adult humans, oral doses of BPA are absorbed by the intestine, and are mostly inactivated (99%) on the first pass through the liver. BPA is mostly metabolized to the metabolite glucuronide, but a sulfate and other metabolites can be produced. Metabolites are eliminated through the urine, but the metabolites clear relatively slowly. The half-life of glucuronide in human blood is about 5.4 hours, but some is still present after 30 hours (Volkel et al. 2002; Vandenberg et al. 2013a). The glucuronide metabolite of BPA is not active in estrogenic assays (Snyder et al. 2000; Matthews et al. 2000; Zalko et al 2003).

Doses from inhalation or dermal absorption reach the liver more slowly, and BPA is inactivated more slowly through these routes. Experiments with dogs show that sublingual absorption might lead to higher levels of free BPA than the oral route through the esophagus (Gayrard et al. 2013).

Infants have immature livers that are not as efficient as adult livers (Vandenberg et al. 2010; 2013a). Toxicokinetics have not been measured in human infants, but metabolism of BPA in neonatal rats is slower

than in adult rats with both oral and non-oral routes of administration. Oral and intravenous doses are inactivated at about the same rate. Slow neonatal metabolism might also be the case for human infants (Taylor et al. 2008). However, inactivation kinetics of oral doses in monkeys are about the same for adults and neonates (Doerge et al. 2010).

Human Experiments

A Volkel et al. (2002) experiment administered BPA to nine human volunteers. They gave a dose of 5 mg BPA 54-90 µg/kg to six people, three men and three women. One of the males and three other males were also given another dose to characterize the kinetics. Doses of BPA were quickly, but not instantaneously inactivated, producing maximum blood levels of the glucuronide metabolite in about 80 minutes. Free BPA levels remained below limits of detection (LOD) in blood (2.28 ng/ml; ppb) and urine (1.37 ng/ml; ppb). The possibility of biological activity at these levels was not discussed, but tissue culture effects have been seen at concentrations more than 1000 times lower (0.23 ppt) (Vom Saal and Hughes 2005).

Critics of the Volkel el al. (2002) article questioned its reliability (80 min and 240 min were both given as times of maximum total BPA blood concentration) (Vandenberg et al. 2010). Many were concerned about a big jump involved in extrapolating the effects from nine individuals to the entire U.S. population. Sick people with bad livers and the elderly may also have slower metabolism. Also, Volkel et al. (2002) administered one acute dose, whereas human environmental exposure is continuous. The kinetics of one dose may not be representative of continuous exposure kinetics and steady state levels (Vandenberg et al. 2010).

Metabolic differences exist between male adults and female adults, fetuses and pregnant women. There is evidence that the human fetus and the placenta may be able to convert the metabolite back to free BPA, although apparently fetal monkeys do not produce free BPA from the conjugate (Ginsberg and Rice 2009; Patterson et al. 2013).

Volkel et al. (2005) administered a smaller dose of BPA (25 µg; 0.28 to 0.43 µg/kg of body weight) to six adults. The limit of detection for BPA was 1.14 ng/ml, and for the glucuronide it was 10.1 ng/ml. In three men 85% of the dose was recovered in urine after 5 hrs, and in the three women 75% of the dose was recovered after this time, mostly as the glucuronide. Urine levels of 1 ng/ml of free BPA were found in two subjects. These subjects had estrogenic BPA in urine, and presumably plasma. Even in this small sample, there were clear differences in BPA metabolism.

Kim et al. (2003) in an experiment with 30 humans found that men eliminated BPA mostly as the glucuronide, with urine concentrations of 2.34 ng/ml, while urine glucuronide concentrations for women were 1.0 ng/ml. BPA in women was metabolized mostly as the sulfate (1.20 ng/ml), while in men the sulfate levels were 0.49 ng/ml.

Even if BPA is inactivated quickly in humans, there may still be time for it to exert an adverse effect. Bae et al. (2015) gave 60 participants over 60 years old beverages that were packaged either in glass bottles or in cans. Urinary BPA concentrations from consumption of beverages in cans were >1600% greater than from glass. Canned beverages caused an average 4.5 mm Hg increase of systolic blood pressure compared to beverages in glass, and the difference was statistically significant. Either BPA caused this increase, or a co-contaminant linked to BPA concentration was responsible.

Since several studies suggest that adult women and men may metabolize BPA differently than pregnant women and children, the Volkel experiments should be extrapolated with caution to these vulnerable populations (Vandenberg et al. 2010).

Free BPA in Blood and Urine

Free BPA in blood and urine is important because it means tissues have been exposed to estrogenic activity. Despite the failure of Volkel et al. (2002; 2005) to find free BPA in blood, and calculations of Teeguarden et al. (2013) based on Fisher et al. (2011) that show little to no free BPA in blood, other studies have shown positive results for free BPA in blood and/or urine.

Vandenberg et al. (2010) reviewed more than 80 human biomonitoring studies in children, adolescents and adults that showed free BPA in blood (ng/ml) and urine, or conjugated BPA in urine (ng/ml). BPA was analyzed in blood and urine by gas chromatography or liquid chromatography (HPLC) coupled to a mass spectrometer. Enzyme linked immunoassay (ELISA) methods were considered less reliable (Dekant and Volkel 2008; Calafat et al. 2008; Calafat et al. 2005). At least 17 studies found free BPA in blood. Means ranged from 0.33 to 2.5 ng/ml (Vandenberg et al. 2010). "The overall consensus that can be determined from blood sampling of healthy adults, adults with certain diseases, pregnant women, and fetuses is that internal exposures to unconjugated BPA are in the range of 0.5-10 ng/ml, with most studies suggesting an average internal exposure of approximately 1-3 ng/ml" (Vandenberg et al. 2007).

Several studies have found free BPA in urine (Calafat et al. 2009; Kim et al. 2003; Volkel et al. 2008; Dekant and Volkel 2008; and others). Since oral doses are converted to the glucuronide, free BPA in urine suggests non-oral exposure or deconjugation reactions in the body have occurred (Vandenberg et al. 2010).

An experiment often cited, Calafat et al. (2008), measured total BPA (free BPA plus metabolites) in the urine of 2,517 people in the U.S. older than 6 years old. About 92.6% had total BPA in their urine at levels ranging from 0.4 to 149 ng/ml (with a mean of 2.6 ng/ml). Children 6-11 had mean levels of 3.6 ng/ml and adolescents 12-19 had levels of 3.7 ng/ml. Calafat et al. 2009 found conjugated BPA in urine of 41 premature babies at mean levels (30.3 ng/ml) that were 11 times higher than the mean for the general population (2.6 ng/ml). Free BPA was found at levels of 1.8 ng/ml. Kinetic models have been used to calculate BPA exposures from urine concentrations, producing estimates ranging from 0.002 to 71.4 µg/kg bw/day (Vandenberg et al. 2010).

In biomonitoring studies such as these, free BPA found in blood and urine might be due to non-enzymatic deconjugation during sample storage. Deconjugation can occur at room temperature in urine samples, but BPA glucuronide in blood samples may be more stable than in urine samples (Dekant and Volkel 2008; Vanderberg et al. 2010). In any BPA experiment, care must be taken to avoid contamination from BPA in water, solvents, and equipment (Ye et al. 2013). Although deconjugation in stored samples is possible, it stretches credibility to believe that all of the biomonitoring results are due to artifacts (Vandenberg et al. 2010).

Conclusion

U.S. regulatory agencies find that BPA is safe at doses below the reproductive toxic threshold of 50 mg/kg bw/day LOAEL, the systemic toxic threshold 5 mg/kg bw/day, or the Reference dose or ADI of 50 µg/kg bw/day. The European Food Safety Authority lowered their ADI to 4 µg/kg bw/day in 2015. These thresholds are mostly based on a few GLP rodent studies and even fewer experiments showing quick inactivation kinetics in humans through oral doses. There is reasonable doubt about the validity of the GLP studies. Among the criticisms are estrogen insensitive test animals, no positive controls, and contaminated control animals. There is also reasonable doubt about extrapolation of kinetic studies performed in nine human subjects to the entire U.S. population. Regulatory findings have also disregarded possible non-dietary exposures.

Biomonitoring studies find free BPA at levels in humans known to cause adverse effects in animals. The regulatory findings tend to dismiss these results as caused by environmental contamination. More than 100 biomonitoring observations have been excluded because they do not agree with the few, small-sample kinetic studies.

Hundreds of in vitro and in vivo experiments that meet well-regarded efficacy criteria have found adverse effects in animals at levels below the toxic threshold. These are peer reviewed studies with a high expectation of validity. Many of the animal experiments are perceived as low weight, or they have been excluded from regulatory evaluation because non-oral doses were used. However, non-oral doses may be valid for evaluation of adverse effects in infants, as their immature livers may detox both oral and non-oral doses slowly.

Human kinetics for BPA in infants have not been measured. Immature rats show slow inactivation of BPA, and monkey experiments show no difference between neonates and adults. Some environmental exposures do not follow the oral kinetics results. Tissue culture experiments are excluded by some regulatory bodies because they cannot easily be associated with known macroscopic adverse reactions. However, they can give biological plausibility to effects seen in animals.

There are about 100 epidemiological studies showing adverse effects in humans. These are given low weight by some because epidemiology may deal with small samples, information that may rely on recall that leads to recall bias, and there may be confounding parameters and general complexity. However, the volume of these reports is a body of evidence that should be considered.

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

Due to concerns about the safety of BPA, some food companies are transitioning to non-BPA products. Canned foods containing BPA include several organic brands, and some of these companies are trying to replace BPA with alternatives (Geller and Lunder 2015). Trasande (2014) has estimated that removing BPA from food products would save the U.S. $1.74 billion in BPA health-related costs.

In 2015, the Environmental Working Group surveyed 119 companies that produce 252 brands. They found that 12% of the brands had replaced BPA in all products. About 14% had replaced BPA in some products. About 31% still had BPA in all products, and 43% gave ambiguous responses. BPA has been removed from many consumer plastic items, such as baby and toddler products, shopping bags, receipts, and frozen meal trays, but finding replacements for metal can liners was found to be more difficult. Companies were not specific about BPA can liner replacements, but many said vinyls, polyesters and oleoresins were the alternatives (Geller and Lunder 2015). More recently, non-BPA epoxy and polyolefins have been introduced. Satisfactory alternatives to BPA exist (Geueke 2016).

Canned food and beverages are packaged in either steel or aluminum cans. Most steel cans are coated with tin to prevent corrosion and rust, but some are coated with chromium. Although fruit is sometimes packaged in tin cans without a protective coating, most tin-coated, chromium-coated, or aluminum cans need a protective layer on the inside to prevent deterioration of food quality. Ideal coatings should be stable, protect the product, adhere to the can, and be flexible to maintain integrity if the can is bent or mashed (Geueke 2016; LaKind 2013).

Historically, the first can coating was oleoresin, a natural mixture of an oil and a resin extracted from various plants, such as pine or balsam fir. Plastic coatings were introduced in the 1940s and 1950s. Coatings include epoxy, vinyl, phenolic, acrylic, polyester and polyolefin (Simal-Gandara 1999; Geueke 2016). Epoxy is the most satisfactory, and has been in general use since 1950. Vinyl coatings do not adhere well to metal, and are often applied as an additional coating on top of another polymer. Vinyl is stable to acidic and alkaline solutions, but it is not heat resistant. Phenolic resins can change the taste of the food, and are not used often. Acrylic is mostly applied as an external coating. Polyester adheres well but is not stable in acidic conditions. Polyolefins are satisfactory coatings that adhere well, are corrosion resistant, and do not change the taste of food (Simal-Gandara 1999; Geueke 2016).

BPA-free epoxy or a polyolefin are generally viewed as preferred alternatives. Other coatings such as polyester, vinyl, and oleoresin might be satisfactory for some uses. However, some consumers might resist polyvinyl because the vinyl chloride monomer is a possible carcinogen (California 2017a; Geueke 2016). Another approach is to use multiple coatings. BPA epoxy is applied to the can, and then a top coating of polyester is applied to prevent BPA migration into food. This latter approach has been used for cans in Japan and twist cap liners in the U.S. (Geueke 2016; Eden Foods 2017).

Glass, stainless steel, high density polyethylene (HDPE), polypropylene, polyphenylsulfone, polyethylene terephthalate (PET), and Tritan copolyester have been used to replace plastics containing BPA in baby

bottles, sippy cups and infant formula applications (Breast Cancer Fund 2010; Kline and Ruhter 2012). More details on these alternative packaging materials and coatings are presented below.

MCF-7 Test for Estrogenicity

Companies seeking to avoid the negative effects of BPA will look for alternatives that do not cause estrogenic problems. One standard test to screen for estrogenicity is the MCF-7 breast cancer proliferation test. Early work was done by Welshons et al. (2003), and the test was refined by George Bittner and associates (Yang et al. 2011; Yang et al. 2014; Bittner et al. 2014ab).

The test is described in Yang et al. (2011). Plastic materials or components are extracted with either salt water or ethanol or both. A number of dilutions of the extracts are then incubated with human breast cancer cells (MCF-7). Estrogenic materials react with estrogen receptors in the cells, activating genes for DNA transcription and cell proliferation. The amount of cell proliferation is a measure of estrogenic activity.

Extract activity was compared to activity of the positive control estradiol (E2) or to untreated controls of distilled water. Estrogenic activity measuring 15% of that of E2 was considered a positive response. If activity was detected, the extract was incubated with ICI, an antiestrogen. The compound was deemed estrogenic only if activity was suppressed by ICI.

At each dilution, the amount of estrogenic activity was defined as relative maximum %E2, or %RME2, the maximum amount of DNA transcription and cell proliferation caused by the chemical, divided by the amount of cell proliferation produced by estradiol at that concentration.

The MCF-7 cell proliferation test is well recognized, and the assay is used on a regular basis (NTP 2016; Soto et al. 2017). The Certi Chem version of the test used by Yang et al. (2011) could be expected to produce valid results for detection of estrogenic activity. Positive controls ensure that the test will detect estrogenic activity. Reaction with antiestrogen ensures that any non-estrogenic materials that might cause cell proliferation are eliminated (Yang et al. 2014).

The Certi Chem MCF-7 test was evaluated by Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternate Toxicological Methods (NICEATAM 2012) (NTP 2016). Reproducibility of the assay was good at three laboratories. Accuracy of the agonist assay (estrogenic activity) was 100% at Certi Chem, 94% at Hiyoshi Corporation, and 88% at Korea Food and Drug Administration (NICEATM 2012).

In a large experiment using the assay, Yang et al. (2011) bought a total of 455 plastic products, many of them designed for food, from various retailers over a three-year period. Some containers were empty, others contained food that was discarded, and the containers were washed with distilled water before testing. Both the empty and the filled containers gave about the same test result.

Some of the products tested represented resin types such as high density polyethylene (HDPE), polypropylene (PP), polycarbonate (PC) and others. Baby bottles, water bottles, rigid containers, flexible containers, plastic bags, and plastic wraps were tested.

Polycarbonate plastics and epoxy resins are made from polymerized BPA. A small amount of BPA does not polymerize, and traces of the monomer BPA leach into the contents of the containers. It was therefore not surprising to find that extracts of plastics such as polycarbonate that contained the estrogenic monomer BPA tested positive for estrogenic activity.

Yang et al. (2011) were surprised to find that about 72% of all the evaluated materials tested positive for estrogenic activity when extracted with either ethanol or saline solution. If the item was extracted with both solvents, 92% of the items tested positive for estrogenic activity. Wagner et al. (2009) also found that bottled water in polyethylene terephthalate (PET) and Tetra Pak™ contained more estrogenic materials than bottled water in glass.

When they tested at 1/100 dilution, saline extracts of polycarbonate bottles containing BPA had more estrogenic activity than bottles containing no BPA. However, when stressed by UV, autoclave or microwave, extracts of non-BPA bottles often tested with higher estrogenic activity than bottles containing BPA.

Since some of the plastics, such as polyethylene, have monomers that are not estrogenic, the authors believed that plastic additives, such as the antioxidant butylated hydroxyl anisole (BHA) might be estrogenic. Subsequent testing showed this to be true. The authors speculated that the detected estrogenic activity is due to phenolic molecule segments in the additives.

A wide range of unstressed plastics showed estrogenic activity. Autoclaving, irradiation with UV light and heating increased the release of estrogenic chemicals. For example, ethanol or saline extracts of an unstressed sample of HDPE showed no estrogenic activity, but HDPE showed 47% estrogenic activity (%RME2) when treated with UV, and then extracted with ethanol.

According to Yang et al. (2011), it is possible to make plastics free of estrogen activity. Polyethylene, polypropylene, copolymers of ethylene and propylene, and plastics constructed of cyclic olefin monomers without additives all tested negative for estrogenic activity. Unprocessed polyacrylamide also showed no estrogenic activity. The authors identified antioxidants and other additives that could be combined with these polymers to produce materials that do not leach estrogenic compounds.

Other researchers have criticized this publication, stating that estrogenic activity in cell cultures does not prove estrogenic activity in an animal or a human. Intact organisms have detoxification systems that protect them (Blake 2014).

Assessments of BPA alternatives may benefit from initial screening in the MCF-7 test. If the material is not estrogenic in this test, it is not likely estrogenic in an intact animal. If it is estrogenic in the MCF-7, further testing is necessary to confirm its safety in humans.

Tritan™

One of the first replacements for BPA to enter the market was Tritan, a polyethylene terephthalate (PET) polyester. Bittner et al. (2014a) tested three Tritan resins using the MCF-7 test and in BG1Luc human cells, and found that Tritan was estrogenic in these tests. The Tritan resins tested were EX401, TX1001 and TX2001. Ethanol (100%) extracts and saline extracts of the unstressed resins were estrogenic. The resins also released estrogenic materials when stressed with ultraviolet light. One of the Tritan additives, triphenylphosphate (TPP), was estrogenic in the tests. TPP had been found estrogenic by other researchers (Kojima et al. 2013).

According to the authors, "our MCF-7 and BG1Luc assays demonstrate that extracts of four unstressed and/or stressed BPA-free thermoplastic resins, one PS [polystyrene] and three Tritan resins, release chemicals that can activate [Estrogen Receptor] ER-dependent cell signaling" (Bittner et al. 2014a). The BG1Luc assay has been validated by ICCVAM, and the MCF-7 assay gave valid results for estrogenic activity in ICCVAM tests (NTP 2016; NICEATM 2012). In other words, the resins tested released chemicals that activated estrogen receptors, producing estrogenic effects in validated human cell culture tests. Estrogenic chemicals cause BG1Luc4E2 human ovarian cancer cells to glow, and MCF-7WS8 human breast cancer cells to proliferate (Bittner et al. 2014a).

Contractors working for Tennessee Eastman, the company that manufactures Tritan, found that the three monomers used in Tritan production were not androgenic or estrogenic in their assays (Osmitz et al. 2012). Tritan monomers had negative estrogenic activity in the uterotrophic assay, and negative androgenic activity in the Hershberger assay. These assays have been validated by ICCVAM (NTP 2016). According to Bittner et al. (2014a), only the 3 monomers used in the Tritan polymer were tested. Unstressed and environmentally stressed Tritan polymers were not tested.

Tennessee Eastman sued George Bittner and his companies, Certi Chem and Plasti Pure, for false advertising, and Eastman won the case. The jury found that positive estrogenic results in cell culture tests did not necessarily mean Tritan would be estrogenic in humans (Blake 2014). The judge and jury did not find the MCF-7 test itself was invalid. Researchers concluded that if a material is not estrogenic in the MCF-7 test, it is not likely estrogenic in humans. If it fails the test, then further testing is needed to prove its safety in humans (Blake 2014).

BPA Analogs: BPB, BPE, BPF, BPS

Structural analogs of BPA are being used to make polymers that provide BPA-free plastic items and plastic coatings for food cans. Bisphenol B (BPB), bisphenol E (BPE), bisphenol F (BPF), bisphenol S (BPS), and 4-cumylphenol have been used to produce BPA-free plastics. BPS has been used in canned soft drinks and foods. BPB has been used in canned tomatoes, soft drinks and beers (Rosenmai et al 2014).

Yang et al. (2011) found that chemicals containing the phenol group were estrogenic in cell culture tests. BPA is estrogenic, but BPA analogs have only recently been investigated for estrogenic properties (Rosenmai et al. 2014).

Rosenmai et al. (2014) tested these analogs in a number of in vitro test systems. "BPA and the five analogues showed a clear effect on AR [androgen receptor] and ER [estrogen receptor] activity as well as on steroid hormone synthesis in the present study, suggesting that these compounds may interfere with the endocrine system through several modes of action." Rosenmai et al. (2014) found "there were indications of DNA damage, carcinogenicity, oxidative stress, effects on metabolism, and skin sensitization of one or more of the test compounds."

Liao and Kannan (2013) found bisphenols in 75% of the U.S. food they sampled. They found that BPA and BPF occurred most frequently, and that canned foods contained higher concentrations than food sold in glass, paper or plastic.

Kinch et al. (2015) found both BPA and BPS at very low levels of exposure caused abnormal neural growth in the developing brains of zebra fish embryos. Exposed zebra fish showed signs of hyperactive behavior. BPA and BPS may have activated zebra fish male hormones that induced the growth. Authors of the study suggest that abnormal neural growth may also occur with humans exposed in utero to BPA and BPS. If true, low level BPA and BPS exposure might be linked to predominately male diseases such as autism and hyperactive behavior (Nutt 2015; Kinch et al. 2015).

Rochester and Bolden (2015) reviewed the literature on hormonal activity of BPS and BPF and found 25 in vivo studies and seven in vitro studies showing that BPS was a likely endocrine disruptor. It had estrogenic, androgenic and other effects, and caused damage to liver DNA. Estrogenic potency was similar to estradiol in membrane receptor models.

Similarly, 4 of 5 in vivo studies showed the analog BPF was estrogenic, androgenic and thyroidogenic. Nineteen in vitro studies also showed these effects, along with other physiological and biochemical effects. The estrogenic potency of BPF and BPS was similar to that of BPA (Rochester and Bolden 2015).

Biomonitoring studies show exposure to BPF and BPS is somewhat less than that of BPA. BPF has been found in 55% of human urine samples at maximum concentrations of 212 ppb, BPS is found 78% of the time up to 12.3 ppb, and BPA is found 95% of the time up to 37.7 ppb (Rochester and Bolden 2015). According to the authors, "because BPS and BPF appear to have metabolism, potencies, and mechanisms of action in vitro similar to BPA, they may pose similar potential health hazards as BPA" (Rochester and Bolden 2015).

BPA Analog: TMBPF

The phenolic group present in all BPA analogs may contribute to their estrogenic activity, as this structure is similar to a phenolic ring in estradiol (Yang et al. 2011). Tetramethylbisphenol F (TMBPF) (CAS 5384-21-4) is a polymer additive that may address this problem by introducing methyl groups adjacent to the

phenolic groups in BPF. The methyl groups may shield the phenolic groups from receptor binding. TMBPF also has limited flexibility in the methylene bridge of its structure, and this rigidity may inhibit receptor binding (Soto et al. 2017).

Neither acetic acid (3%) nor ethanol (50%) extracts of the monomer or the polymer produced from TMBPF are active in the MCF-7 estrogenic test. TMBPF does not activate the estrogen receptor or cause MCF-7 cell proliferation. It is not active in the uterotropic assay (activity is associated with weight gain in the rodent uterus upon exposure to the test material). TMBPF does not alter time to puberty in either female or male rats (Soto et al. 2017).

Polymer production leaves no unreacted monomer in the final matrix. TMBPF migration from polymer to food simulants was below the level of detection of 0.2 ppb (Soto et al. 2017).

Polymers made from TMBPF may provide the estrogenic free, biologically inactive plastic that could be used to coat food cans (Soto et al. 2017). The polymer is being marketed by Valspar as valPure™, non-BPA epoxy (Geueke 2016).

Cyclic Olefins, Nylon, PETG

Bittman et al. (2014a) found that ten plastics: four cyclic olefin copolymers (COC), one cyclic olefin polymer (COP), one nylon polymer, and four glycol modified polyethylene terephthalate (PETG) polymers released no estrogenic substances when extracted with saline or ethanol. Extracts were tested using the MCF-7 cell proliferation test and the BG1Luc assay.

Yang et al. (2011) found polyethylene, polypropylene, copolymers of ethylene and propylene, and plastics constructed of cyclic olefin monomers without additives tested negative for estrogenic activity. Unprocessed polyacrylamide also showed no estrogenic activity.

Polyolefin can coatings are being sold under the brand name Canvera™. According to the Food Packing Forum, the coating exhibits corrosion protection, flexibility and adhesion, and does not affect food quality (Geueke 2016).

Oleoresin

The first can coatings were made of oleoresins, which are mixtures of oils and resins extracted from plants. These were replaced by epoxy coatings about 1950. Oleoresins do not adhere well to cans, and their corrosion resistance is limited. They are appropriate for mild foods such as beans (Geueke 2016). Eden Foods is now using oleoresin coatings to replace BPA coatings. They are used for such products as beans and chili, but oleoresins cost 21-34% more than epoxy coatings (Eden Foods 2017).

Glass Jars

Another approach is to abandon metal cans and move products into glass packaging. There is a long history of home canning in glass Mason jars. However, the metal cap for the twist seal still has to be treated with some kind of protective coating. Eden Foods uses amber glass jars for corrosive products such as canned tomatoes. The lids for the twist caps are treated with a multilayer of epoxy and another polymer (Eden Foods 2017).

Bioplastics

Bioplastics have the advantages that they can be obtained from renewable sources, and they can be composted. The disadvantages are that they are less chemically stable than products such as polyolefins, and they may be hydrolyzed by water. To maintain a reasonable shelf life, antioxidants and other materials must be added to the polymer. Biopolymers may also be brittle, may not be good barriers to gases, and may undergo thermal distortion. Bioplastics generally are not good candidates for can liners (Siracusa et al. 2008; Rhim et al. 2013).

Polylactic acid (PLA) is currently used in food packaging. PLA is a recyclable, transparent polymer with good resistance to water solubility. It is currently used in food packaging for short shelf life materials. One

brand name is Natureworks™ PLA. Problems with PLA include brittleness, and it is not a good barrier to gases and vapors. Another problem with PLA is that the finished polymer may be estrogenic. Yang et al. (2011) tested several samples of PLA and found that 91% of the samples were estrogenic in the MCF-7 cell proliferation test when extracted with either ethanol or saline.

Starch based polymers may be suitable for some uses. These have been commercialized under brand names such as EcoStar™ and BioPlast™. Starch polymers are used in food trays (Siracusa et al. 2008).

Evidence indicates that some of the negative properties of biopolymers can be addressed with the addition of nanoparticles of clay or silica. More research is needed before these materials can be recommended as BPA alternatives. According to Rhim et al. (2013), nanoparticles from packaging may end up in food, and nanoparticles can be toxic to human cells. They can cross cellular barriers and can lead to oxidative damage and inflammatory reactions. There are concerns about accumulations in the brain and other organs, and in developing fetuses. According to Rhim et al. 2013, "The risk assessment of nanomaterials after ingestion has been studied only for few of the nanoparticles used in food packaging."

Conclusion

Alternatives are available for can coatings containing BPA. Some of these are economical and as functional as BPA epoxy coatings. Practical options include polyolefin or non-BPA, nonestrogenic epoxy. For some applications, oleoresin, polyester, or polyvinyl coatings are possible solutions. Oleoresin coatings are more costly than other alternatives. Non-estrogenic plastics such as polyethylene, polypropylene, copolymers of ethylene and propylene, and plastics constructed of cyclic olefin monomers are available to replace polycarbonate and other plastic containers that release estrogenic materials.

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)).

Oleoresin is a natural material that may be used as an alternative to BPA. See above for more information about this substance.

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

There are no organic agricultural products that could be alternatives to BPA plastics (Siracusa et al. 2008; Rhim et al. 2013).

References

Akingbemi, B.T., C.M. Sottas, A.I. Koulova et al. "Inhibition of Testicular Steroidogenesis by the Xenoestrogen Bisphenol A is Associated with Reduced Pituitary Luteinizing Hormone Secretion and Decreased Steroidogenic Enzyme Gene Expression in Rat Leydig Cells. *Endocrinol*. 145, No. 2, (2004): 592-603.

Alonso-Magdalena, P., A.B. Ropero, S. Soriano et al. "Bisphenol A: A New Diabetogenic Factor?" *Hormones* 9, No. 2, (2010): 118-126.

Ashby, J., H. Tinwell and J. Haseman. "Lack of Effects for Low Dose Levels of Bisphenol A and Diethylstilbestrol on the Prostate Gland of CF1 Mice Exposed in utero." *Regul. Toxicol. Pharmacol*. 30, (1999): 156-166.

Bae, S., and Y.C. Hong. "Exposure to Bisphenol A from Drinking Canned Beverages Increases Blood Pressure, Randomized Crossover Trial." *Hypertension* 65, (2015): 313-319.

Berger, R.G., J. Shaw and D. deCatanzaro. "Impact of Acute Bisphenol-A Exposure upon Intrauterine Implantation of Fertilized Ova and Urinary Levels of Progesterone and 17beta-Estradiol." *Repro. Toxicol*. 26, (2008): 94-99.

Benachour, N. and A. Aris. "Toxic Effects of Low Doses of Bisphenol-A on Human Placental Cells." *Toxicol. Appl. Pharmacol*. 241, (2009): 322-328.

Bittner, G.D., M.S. Denison, C.Z. Yang et al. "Chemicals Having Estrogenic Activity can be Released from some Bisphenol A-Free, Hard and Clear, Thermoplastic Resins." *Environ. Health* 13, (2014a): 103. 18 pp.

Bittner, G.D., C.Z. Yang and M.A. Stoner. "Estrogenic Chemicals often Leach from BPA-free Plastic Products that are Replacements for BPA-Containing Polycarbonate Products." *Environ. Health* 13, (2014b): 41. 15 pp.

Blake, M. 2014. "The Scary New Evidence on BPA free Plastics." *Mother Jones*. March 3, 2014. www.motherjones.com/environment/.../tritan-certichem-eastman-bpa-free-plastic-safe

Bonefeld-Jorgensen, E.C., M. Long, M.V. Hofmeister et al. "Endocrine-Disrupting Potential of Bisphenol A, Bisphenol A Dimethacrylate, 4-n-Nonylphenol, and 4-n-Octylphenol in Vitro: New Data and a Brief Review." *Environ. Health Perspect*. 115, Suppl. 1, (2007): 69-76.

Borrirukwisitsak, S., H.E. Keenan and C. Gauchotte-Lindsay. "Effects of Salinity, pH and Temperature on the Octanol-Water Partition Coefficient of Bisphenol A. *Intl. J. Environ. Sci. Devel.* 3, no. 5, (2012): 460-464.

Braun, J.M., K. Yolton, K.N. Dietrich et al. "Prenatal Bisphenol A Exposure and Early Childhood Behavior." *Environ. Health Perspect*. 117, (2009): 1945-1952.

Braun, J.M., A.E. Kalkbrenner, A.M. Calafat et al. "Impact of Early-Life Bisphenol A Exposure on Behavior and Executive Function in Children." *Pediatrics* 128, (2011): 873-882.

Breast Cancer Fund. 2010. "Safer Alternatives to Bisphenol A (BPA)." Breast Cancer Fund, February 17, 2010, 4pp. www.breastcancerfund.org

Cagen, S.Z., J.M. Waechter, Jr., S.S. Dimond et al. "Normal Reproductive Organ Development in CF-1 Mice Following Prenatal Exposure to Bisphenol A." *Toxicol. Sci.* 50, (1999): 36-44.

Calafat, A.M., Z. Kuklenyik, J.A. Reidy et al. "Urinary Concentrations of Bisphenol A and 4-Nonylphenol in a Human Reference Population." *Environ. Health Perspect*. 113, (2005): 391-395.

Calafat, A.M., X. Ye, L.Y. Wong et al. "Exposure of the U.S. Population to Bisphenol A and 4-tertiary-Octylphenol: 2003-2004." *Environ. Health Perspect*. 116, (2008): 39-44.

Calafat, A.M., J. Weuve, X. Ye et al. "Exposure to Bisphenol A and Other Phenols in Neonatal Intensive Care Unit for Premature Infants." *Environ. Health Perspect*. 117, (2009): 639-644.

California. 2017a. "Chemicals Known to the State to Cause Cancer or Reproductive Toxicity." State of California, Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Drinking Water and Toxic Enforcement Act of 1986. January 27, 2017.

California. 2017b. "Canned or Bottled Foods where BPA was Intentionally Used in the Manufacture of the Can Lining, Bottle Seals, or Jar Lids. Office of Environmental Health Hazard Assessment." https://www.p65warnings.ca.gov/bpalist

Canada. 2014. "Bisphenol A." Health Canada. http://www.hc-sc.gc.ca/fn-an/securit/packag-emball/bpa/index-eng.php

Canada. 2015. "National Standard of Canada, Organic Production Systems Permitted Substances Lists." *CAN/CGSB-32.311-2015. 82 pp.* https://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/programme-program/normes-standards/internet/bio-org/documents/lsp-psl-eng.pdf

Canada. 2017. "Chemical Substances in Batch 2 of the Challenge. Final Order Adding One Substance (bisphenol A)." Canada Gazette, part II, vol. 144, no. 21, October 13, 2010. http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-2/index-eng.php

Cao, X.L., G. Dufresne, S. Belisle et al. "Levels of Bisphenol A in Canned Liquid Infant Formula Products in Canada and Dietary Intake Estimates." *J. Agric. Food Chem.* 56, (2008): 7919-7924.

Carwile, J.L., X.Y. Ye, X.L. Zhou et al. "Canned Soup Consumption and Urinary Bisphenol A: a Randomized Crossover Trial." *JAMA* 306, No. 20, (2011): 2218-2219.

Chitra, K.C., L. Latchoumycandane and P.P. Mathur. "Induction of Oxidative Stress by Bisphenol A in the Epididymal Sperm of Rats." Toxicol. 185, (2003): 119-127.

Christensen, K.L.Y., M. Lorber, S. Koslitz et al. "The Contribution of Diet to Total Bisphenol A Body Burden in Humans: Results of a 48 Hour Fasting Study." *Environ. Intl.* 50, (2012): 7-14.

Churchwell, M.I., L. Camacho, M.M. Vanlandingham et al. "Comparison of Life-Stage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague Dawley Rats." *Toxicol. Sci.* 139, No. 1, (2014): 4-20.

Codex Alimentarius. 2001. *Codex Alimentarius: Organically Produced Foods*. Joint FAO/WHO Food Standards Programme, Codex Alimentarius Commission, Rome, Italy. 73 pp. ftp://ftp.fao.org/docrep/fao/005/Y2772e/Y2772e.pdf

Colburn, T., D. Dumanoski, J.P. Myers. *Our Stolen Future.* New York, NY: Penguin Books, 1996.

Consumers Union. 2014. "State Bans on BPA." http://consumersunion.org/research/progress-in-protecting-our-children/

Corbel, T., E. Perdu, V. Gayrard et al. "Conjugation and Deconjugation Reactions within the Fetoplacental Compartment in a Sheep Model: A Key Factor Determining Bisphenol A Fetal Exposure." *Drug Metab. Disposition* 43, (2015): 467-576.

Crain, D.A., M. Eriksen, T. Iguchi et al. "An Ecological Assessment of Bisphenol-A: Evidence from Comparative Biology." *Reprod. Toxicol.* 24, (2007): 225-239.

Dekant, W. and W. Volkel. "Human Exposure to Bisphenol A by Biomonitoring: Methods, Results, and Assessment of Environmental Exposures." *Toxicol. Appl. Pharmacol.* 228, (2008): 114-134.

Delclos, K.B., L. Camacho, S.M. Lewis et al. "Toxicity Evaluation of Bisphenol A Administered by Gavage to Sprague Dawley Rats from Gestation Day 6 Through Postnatal Day 90." *Toxicol. Sci.* 139, No. 1, (2014): 174-197.

Dodds, E.C. and W. Lawson. "Synthetic Oestrogenic Agents without the Phenanthrene Nucleus." *Nature* 137, (1936): 996, June 13, 1936.

Doerge, D.R., N.C. Twaddle, K.A. Woodling et al. "Pharmacokinetics of Bisphenol A in Neonatal and Adult Rhesus Monkeys." *Toxicol. Appl. Pharmacol.* 248, (2010): 1-11.

Eden Foods. 2017. "Eden Foods Bisphenol A (BPA)-Free Pioneer." http://www.edenfoods.com/articles/view.php?articles_id=178

Ejaredar, M., Y. Lee, D.J. Roberts et al. "Bisphenol A Exposure and Children's Behavior: A Systematic Review." *J. Expos. Sci. Environ. Epidemiol.* 27, (2017): 175-183.

Edginton, A.N. and L. Ritter. "Predicting Plasma Concentrations of Bisphenol A in Children Younger than 2 Years of Age after Typical Feeding Schedules, using a Physiologically Based Toxicokinetic Model. *Environ. Health Perspect.* 117, (2009): 645-652.

EFSA (European Food Safety Authority). 2015. "Scientific Opinion on the Risks to Public Health Related to Bisphenol A (BPA) in Foodstuffs." *EFSA Journal* 13(1): 3978. 1040 pp.

Ema, M., S. Fujii, M. Furukawa et al. "Rat Two-Generation Reproductive Toxicity Study of Bisphenol A." *Reprod. Toxicol.* 15, (2001): 505-523.

EU ECC. 2007. "Council Regulation (EC) No. 834/2007 of 28 June 2007." *Official Journal of the European Union* 189 (2007): 1-22. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:189:0001:0023:EN:PDF

EU ECC. 2008. "Commission Regulation (EC) No. 889/2008 of 5 September 2008." *Official Journal of the European Union* 250 (2008): 1-84. eur-lex.europa.eu/legal-content/EN/ALL/?uri=OJ:L:**2008**:250...

EU. 2011. "Commission Implementing Regulation (EU) No 321/2011 of 1 April 2011, Amending Regulation 10/2011 as Regards the Restriction of Use of Bisphenol A in Plastic Infant Feeding Bottles." http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R0321&from=EN

EU. 2016. "Commission Regulation (EU) 2016/2235 of 12 December 2016." http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R2235&from=EN

Fernandez, M., N. Bourguignon, V. Lux-Lantos et al. "Neonatal Exposure to Bisphenol A and Reproductive and Endocrine Alterations Resembling the Polycystic Ovarian Syndrome in Adult Rats." *Environ. Health Perspect*. 118, (2010): 1217-1222.

Fiege, H., H.W. Voges, T. Hamamoto et al. "Phenol Derivatives." *Ullmann's Encyclopedia of Industrial Chemistry.* (Weinheim: Wiley-VCH, 2000), pp. 521-576.

Fisher, J.W., N.C. Twaddle, M. Vanlandingham et al. "Pharmacokinetic Modeling: Prediction and Evaluation of Route Dependent Dosimetry of Bisphenol A in Monkeys with Extrapolation to Humans." *Toxicol. Appl. Pharmacol.* 257, (2011): 122-136.

Gayrard, V., M.Z. Lacroix, S.H. Collet et al. "High Bioavailability of Bisphenol A from Sublingual Exposure." *Environ. Health Perspect.* 121, (2013): 951-956.

Geller, S. and S. Lunder. 2015. "BPA in Canned Food: Behind the Brand Curtain." Environmental Working Group. May 2015. 52 pp. http://static.ewg.org/reports/2015/bpa_in_canned_food/BPA-in-canned-food.pdf?_ga=1.22449019.1708941459.1487106792

Geueke, B. "Dossier—Can Coatings." Food Packaging Forum. December 2016. 10 pp. *www.foodpackagingforum.org/fpf-2016/wp.../FPF_Dossier11_can-coatings-1.pdf*

Ginsberg, G. and D.C. Rice. "Does Rapid Metabolism Ensure Negligible Risk from Bisphenol A?" *Environ. Health Perspect*. 117, (2009): 1639-1643.

Goncalves, M.R., R.W. Cunha, D.M. Barros et al. "Effects of Prenatal and Postnatal Exposure to a Low Dose of Bisphenol A on Behavior and Memory in Rats." *Environ. Toxicol. Pharmacol.* 30, (2010): 195-201.

Goodman, J.E., R.J. Witorsch, E.E. McConnell et al. "Weight-of-Evidence Evaluation of Reproductive and Developmental Effects of Low Doses of Bisphenol A." *Crit. Rev. Toxicol*. 39, (2009): 1-75.

Gray, G.M., J.T. Cohen, G. Cunha et al. "Weight of the Evidence Evaluation of Low-Dose Reproductive and Developmental Effects of Bisphenol A." *Human Ecol. Risk Assess*. 10, (2004): 875-921.

Hengstler, J.G., H. Foth, T. Gebel et al. "Critical Evaluation of Key Evidence on the Human Health Hazards of Exposure to Bisphenol A." *Crit. Rev. Toxicol*. 41, No. 4, (2011): 263-291.

Ho, S.M., W.Y. Tang, J. Belmonte de Frausto et al. "Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4." *Cancer Res*. 66, No. 11, (2006): 5624-5632.

Honma, S., A. Suzuki, D.L. Buchanan et al. "Low Dose Effect of in utero Exposure to Bisphenol A and Diethylstilbestrol on Female Mouse Reproduction. *Reproduct. Toxicol*. 16, (2002): 117-122.

Howdeshell, K.L., R.H. Peterman, B.M. Judy et al. "Bisphenol A is Released from Used Polycarbonate Animal Cages into Water at Room Temperature." *Environ. Health Perspect*. 111, (2003): 1180-1187.

Hunt, P.A., C. VandeVoort, T. Woodruff et al. "Invalid Controls Undermine Conclusions of FDA Studies." *Toxicol. Sci*. 141, No. 1, (2014): 2.

IFOAM (International Federation of Organic Agriculture Movements). 2012. *IFOAM Norms for Organic Production and Processing*. 32 pp.
www.ifoam.bio/.../ifoam_norms_version_august_2012_with_cover.pdf

JAS (Japanese Agricultural Standard). 2005. "Japanese Agricultural Standard of Organic Agricultural Products." 8 pp. www.cei.org.ni/.../Estándares%20_%20Japón%20_%20Prod_%20Agri_ %20Organicos.pdf

Johns, L.E., K.K. Ferguson and J.D. Meeker. "Relationships between Urinary Phthalate Metabolite and Bisphenol A Concentrations and Vitamin D Levels in U.S. Adults: National Health and Nutrition Examination Survey (NHANES), 2005-2010." *J. Clin. Endocrinol. Metab.* 101, (2016): 4062-4069.

Kang, J.H., K. Kito and F. Kondo. "Factors Influencing the Migration of Bisphenol A from Cans." *J. Food Prot.* 66, No. 8, (2003): 1444-1447.

Kang, J.H., F. Kondo and Y. Katayama. "Human Exposure to Bisphenol A." *Toxicol.* 226, (2006): 79-89.

Keri, R.A., S.M. Ho, P.A. Hunt et al. "An Evaluation of Evidence for the Carcinogenic Activity of Bisphenol A." *Reprod. Toxicol*. 24, (2007): 240-252.

Kim, Y.H., C.S. Kim, S. Park et al. "Gender Differences in the Levels of Bisphenol A Metabolites in Urine." *Biochem. Biophys. Res. Comm*. 312, (2003): 441-448.

Kinch, C.D., K. Ibhazehiebo, J.H. Jeong et al. "Low Dose Exposure to Bisphenol A and Replacement Bisphenol S Induces Precocious Hypothalamic Neurogenesis in Embryonic Zebrafish." *PNAS* 112, No. 5, (2015): 1475-1480.

Kline, T.R. and M.C. Ruhter. 2012. "Alternatives Analysis Report for Bisphenol A in Infant Formula Cans and Baby Food Jar Lids." Techlaw Inc, 49 New Concord Road, East Chatman, NY. 156 pp.

Kojima, H., S. Takeuchi, T. Itoh et al. "In vitro Endocrine Disruption Potential of Organophosphate Flame Retardants via Human Nuclear Receptors." *Toxicol.* 314, (2013): 76-83.

Krishnan, A.V., P. Stathis, S.F. Permuth et al. "Bisphenol A: An Estrogenic Substance is Released from Polycarbonate Flasks during Autoclaving." *Endocrinol.* 132, (1993): 2279-2286.

Kubo, K., O. Arai, M. Omura et al. "Low Dose Effects of Bisphenol A on Sexual Differentiation of the Brain and Behavior in Rats." *Neurosci. Res.* 45, (2003): 345-356.

LaKind, J.S. "Can Coatings for Foods and Beverages: Issues and Options." *Intl. J. Technol., Policy, Management* 13, No. 1, (2013): 80-94.

Lang, I.A., T.S. Galloway, A. Scarlett et al. "Association of Urinary Bisphenol A Concentration with Medical Disorders and Laboratory Abnormalities in Adults." *JAMA* 300, No 11, (2008): 1303-1310.

Leranth, C., T. Hajszan, K. Szigeti-Buck et al. "Bisphenol A Prevents the Synaptogenic Response to Estradiol in Hippocampus and Prefrontal Cortex of Ovariectomized Nonhuman Primates." *PNAS* 105, No. 37, (2008): 14187-14191.

Liao, C. and K. Kannan. "Concentrations and Profiles of Bisphenol A and Other Bisphenol Analogues in Foodstuffs from the United States and their Implications for Human Exposure." *J. Agric. Food Chem.* 61, (2013): 4655-4662.

Markey, C.M., P.R. Wadia, B.S. Rubin et al. "Long-Term Effects of Fetal Exposure to Low Doses of the Xenoestrogen Bisphenol-A in the Female Mouse Genital Tract." *Biol. Reproduction* 72, (2005): 1344-1351.

Masuno, H., J. Iwanami, T. Kidani et al. "Bisphenol A Accelerates Terminal Differentiation of 3T3-L1 Cells into Adipocytes through Phosphtidylinositol 3-Kinase Pathway." *Toxicol. Sci.* 84, (2005): 319-327.

Matthews, J.B., K. Twomey and T.R. Zacharewski. "In vitro and in vivo Interactions of Bisphenol A and its Metabolite, Bisphenol A Glucuronide, with Estrogen Receptors Alpha and Beta." *Chem. Res. Toxicol.* 14, No. 2, (2001): 149-157.

Melnick, R., G. Lucier, M. Wolfe et al. "Summary of the National Toxicology Program's Report of the Endocrine Disruptors Low-Dose Peer Review." *Environ. Health Perspect.* 110, (2002): 427-431.

Miyawaki, J., K. Sakayama, H. Kato et al. "Perinatal and Postnatal Exposure to Bisphenol A Increases Adipose Tissue Mass and Serum Cholesterol Level in Mice. *J. Atheroscler. Thromb.* 14, (2007): 245-252.

Moriyama, K., T. Tagami, T. Akamizu et al. "Thyroid Hormone Action is Disrupted by Bisphenol A as an Antagonist." *J. Clin. Endocrinol. Metab.* 87, (2002): 5185-5190.

Munoz-de-Toro, M., C.M. Markey, P.R. Wadia et al. "Perinatal Exposure to Bisphenol-A Alters Peripubertal Mammary Gland Development." *Endocrinol.* 146, No. 9. (2005): 4138-4147.

Murray, T.J., M.V. Maffini, A.A. Ucci et al. "Induction of Mammary Gland Ductal Hyperplasias and Carcinoma in situ Following Fetal Bisphenol A Exposure." *Reprod. Toxicol.* 23, No. 3, (2007): 383-390.

Myers, J.P., F.S. Vom Saal, B.T. Akingbemi et al. "Why Public Health Agencies Cannot Depend on Good Laboratory Practices as a Criterion for Selecting Data: The Case of Bisphenol A." *Environ. Health Perspect.* 117, No. 3, (2009a): 309-315.

Myers, J.P., R.T. Zoeller and F.S. Vom Saal. "A Clash of Old and New Scientific Concepts in Toxicity, with Important Implications for Public Health." *Environ. Health Perspect.* 117, No. 11, (2009b): 1652-1655.

Nagel, S.C., F.S. vom Saal, K.A. Thayer et al. "Relative Binding Affinity-Serum Modified Access (RBA-SMA) Assay Predicts the Relative in vivo Bioactivity of the Xenoestrogens Bisphenol A and Octylphenol." *Environ. Health Perspect*. 105, (1997): 70-76.

Neagu, L. 1998. *Synthesis of Bisphenol A with Hetereogeneous Catalysts*. Master of Science in Engineering Thesis, Queen's University, Kingston, Ontario, Canada, August, 1998. 184 pp.

Newbold, R.R., W.N. Jefferson and E. Padilla-Banks. "Prenatal Exposure to Bisphenol A at Environmentally Relevant Doses Adversely Affects the Murine Female Reproductive Tract Later in Life." *Environ. Health Perspect.* 117, (2009): 879-885.

NICEATM. 2012. "Draft Validation Study Report, MCF-7 Cell Proliferation Test Method." National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). June 18, 2012. 40 pp. https://ntp.niehs.nih.gov/iccvam/methods/endocrine/mcf7/mcf7-valstudyreport-19jun12-wcv2-draft.pdf

Noonan, G.O., L.K. Ackerman and T.H. Begley. "Concentration of Bisphenol A in Highly Consumed Canned Foods in the U.S. Market." *J. Agric. Food Chem*. 59, (2011): 7178-7185.

NTP. 1982. "NTP Technical Report on the Carcinogenesis Bioassay of Bisphenol A (CAS No. 80-05-7) in F344 Rats and B6C3F1 Mice (Feed Study)." National Toxicology Program, Research Triangle Park, North Carolina and Bethesda, Maryland. NIH Pub. No. 82-1771. 131 pp.

NTP. 2008. "NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A." Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program. NIH Pub. No. 08-5994. 321 pp.

NTP. 2016. "Endocrine Disruptor Test Method Evaluations." National Toxicology Program. *https://ntp.niehs.nih.gov/pubhealth/evalatm/test-method.../endocrine-disruptors/*

Nutt, A.E. 2015. "BPA Alternative Disrupts Normal Brain-cell Growth, is Tied to Hyperactivity, Study Says." *Washington Post*, January 12, 2015. https://www.washingtonpost.com/national/health-science/bpa-alternative-disrupts-normal-brain-cell-growth-is-tied-to-hyperactivity-study-says/2015/01/12/a9ecc37e-9a7e-11e4-a7ee-526210d665b4_story.html?utm_term=.9babaaac77a7

Osimitz, T.G., M.L. Eldridge, E. Sloter et al. "Lack of Androgenicity and Estrogenicity of the Three Monomers used in Eastman's Tritan™ Copolyesters." *Food Chem. Toxicol.* 50, (2012): 2196-2205.

Palanza, P. K.L. Howdeshell, S. Parmigiani et al. "Exposure to a Low Dose of Bisphenol A During Fetal Life or in Adulthood Alters Maternal Behavior in Mice." *Environ. Health Perspect.* 110, Suppl. 3, (2002): 415-422.

Palanza, P., L. Gioiosa, F.S. vom Saal et al. "Effects of Developmental Exposure to Bisphenol A on Brain and behavior in Mice." *Environ. Res.* 108, (2008): 150-157.

Patterson, T.A., N.C. Twaddle, C.S. Roegge et al. "Concurrent Determination of Bisphenol A Pharmacokinetics in Maternal and Fetal Rhesus Monkeys." *Toxicol. Appl. Pharmacol.* 267, (2013): 41-48.

Rhim, J.W., H.M. Park and C.S. Ha. "Bio-Nanocomposites for Food Packaging Applications." *Prog. Polymer Sci.* 38, (2013): 1629-1652.

Richter, C.A., L.S. Birnbaum, F. Farabollini et al. "In vivo Effects of Bisphenol A in Laboratory Rodent Studies." *Reprod. Toxicol.* 24, No. 2, (2007): 199-224.

Rochester, J.R. "Bisphenol A and Human Health: A Review of the Literature." *Reprod. Toxicol.* 42, (2013): 132-155.

Rochester, J.R. and A.L. Bolden. "Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes." *Environ. Health Perspect.* 123, (2015): 643-650.

Rosenmai, A.K., M. Dybdahl, M. Pedersen et al. "Are Structural Analogues to Bisphenol A Safe Alternatives?" *Toxicol. Sci.* 139, No. 1, (2014): 35-47.

Rubin, B.S., M.K. Murray, D.A. Damassa et al. "Perinatal Exposure to Low Doses of Bisphenol A Affects Body Weight, Patterns of Estrous Cyclicity, and Plasma LH Levels." *Environ. Health Perspect.* 109, (2001): 675-680.

Rubin, B.S. and A.M. Soto. "Bisphenol A: Perinatal Exposure and Body Weight." *Mol. Cellular Endocrinol.* 304, (2009): 55-62.

Rudel, R.A., S.J. Melly, P.W. Geno et al. "Identification of Alkylphenols and Other Estrogenic Phenolic Compounds in Wastewater, Septage, and Groundwater on Cape Cod, Massachusetts." *Environ. Sci. Technol.* 32, (1998): 861-869.

Signorile, P.G., E.P. Spugnini, L. Mita et al. "Pre-natal exposure of Mice to Bisphenol A Elicits an Endometriosis-Like Phenotype in Female Offspring." *Gen. Compar. Endocrinol.* 168, (2010): 318-325.

Simal-Gandara, J. "Selection of Can Coatings for Different Applications." *Food Rev. Intl.* 15, No. 1, (1999): 121-137.

Siracusa, V., P. Rocculi, S. Romani et al. "Biodegradable Polymers for Food Packaging: a Review." *Trends Food Sci. Technol.* 19, (2008): 634-643.

Snyder, R.W., S.C. Maness, K.W. Gaido et al. "Metabolism and Disposition of Bisphenol A in Female Rats." *Toxicol. Appl. Pharmacol.* 168, (2000): 225-234.

Soto, A.M., L.N. Vandenberg, M.V. Maffini et al. "Does Breast Cancer Start in the Womb?" *Basic Clin. Pharmacol. Toxicol.* 102. (2008): 125-133.

Soto, A.M., C. Schaeberle, M.S. Maier et al. "Evidence of Absence: Estrogenicity Assessment of a New Food Contact Coating and the Bisphenol Used in its Synthesis." *Environ. Sci. Technol.* 51, (2017): 1718-1726.

Sowlat, M.H., S. Lotfi, M. Yunesian et al. "The Association Between Bisphenol A Exposure and Type-2 Diabetes: A World Systematic Review." *Environ. Sci. Pollut. Res.* 23, (2016): 21125-21140.

Spanier, A.J., R.S. Kahn, A.R. Kunselman et al. "Prenatal Exposure to Bisphenol A and Child Wheeze from Birth to 3 Years of Age." *Environ. Health Perspect.* 120, (2012): 916-920.

Takao, T., W. Nanamiya, I. Nagano et al. "Exposure with the Environmental Estrogen Bisphenol A Disrupts the Male Reproductive Tract in Young Mice." *Life Sci.* 65, No. 22, (1999): 2351-2357.

Taylor, J.A., W.V. Welshons and F.S. vom Saal. "No Effect on Route of Exposure (Oral; Subcutaneous Injection) on Plasma Bisphenol A throughout 24 h after Administration in Neonatal Female Mice. *Reprod. Toxicol.* 25, (2008): 169-176.

Teeguarden, J., S. Hanson-Drury, J.W. Fisher et al. "Are Typical Human Serum BPA Concentrations Measurable and Sufficient to be Estrogenic in the General Population?" *Food Chem. Toxicol.* 62, (2013): 949-963.

Toyama, Y., F. Suzuki-Toyota, M. Maekawa et al. "Adverse Effects of Bisphenol A to Spermiogenesis in Mice and Rats." *Arch. Histol. Cytol.* 67, No. 4, (2004): 373-381.

Trasande, L., T.M. Attina and J. Blustein. "Association Between Urinary Bisphenol A Concentration and Obesity Prevalence in Children and Adolescents." *JAMA* 308, No. 11, (2012): 1113-1121.

Trasande, L. "Further Limiting Bisphenol A in Food Uses Could Provide Health and Economic Benefits." *Health Affairs* 33, No. 2, (2014): 1-7.

Tyl, R.W., C.B. Myers, M.C. Marr et al. "Three Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD Sprague-Dawley Rats." *Toxicol. Sci.* 68, (2002): 121-146.

Tyl, R.W., C.B. Myers, M.C. Marr et al. "Two Generation Reproductive Toxicity Evaluation of Dietary 17beta-Estradiol (E2, CAS no. 50-28-2) in CD-1 (Swiss) Mice." *Toxicol. Sci.* 102, No. 2, (2008a): 392-412.

Tyl, R.W., C.B. Myers, M.C. Marr et al. "Two-Generation Reproductive Toxicity Study of Dietary Bisphenol A in CD-1 (Swiss) Mice." *Toxicol. Sci.* 104, No. 2, (2008b): 362-384.

Tyl, R.W. "Basic Exploratory Research Versus Guideline Compliant Studies used for Hazard Evaluation and Risk Assessment: Bisphenol A as a Case Study. *Environ. Health Perspect.* 117, (2009): 1644-1654.

USDA. 2013. "USDA Foreign Agricultural Service Gain Report No. FR9133: French Law Banning BPA in Food Containers Enacted." February 6, 2013. https://gain.fas.usda.gov/Recent%20GAIN%20Publications/French%20Law%20Banning%20Bisphenol%20A%20in%20Food%20Containers%20Enacted_Paris_France_2-5-2013.pdf

USDA NOSB 2014a. "National Organic Standards Board Materials Subcommittee Research Priorities for 2014." August 26, 2014. 9 pp. https://www.ams.usda.gov/sites/default/.../MSResearchPrioritiesProposalOct2014.pdf

USDA NOSB 2014b. "Memorandum to the National Organic Standards Board (NOSB) on Packaging Substances used in Organic Food Handling." November 19, 2014. 4 pp. https://www.ams.usda.gov/sites/default/files/media/NOSB%20Memo%20Packaging%20Substances%20used%20in%20organic%20food.pdf

USDA NOSB 2015. "Memorandum to the National Organic Standards Board (NOSB) on National Organic Standards Board Recommendations (October 2014)." 4 pp. https://www.ams.usda.gov/sites/default/files/media/NOSB%20Memo%20Response%20to%20Rec%20from%20Oct%202014%20Meeting.pdf

USDA NOSB 2017a. "National Organic Standards Board (NOSB) Handling Subcommittee Meeting Notes," January 3, 2017. https://www.ams.usda.gov/sites/default/files/media/HSNotes2017Jan.pdf

USDA NOSB 2017b. "National Organic Standards Board Handling Subcommittee, Bisphenol A (BPA) in Packaging Discussion Document." pp. 47-53 in Agenda for NOSB meeting, April 19-21 in Denver, CO. February 21, 2017. https://www.ams.usda.gov/sites/default/files/media/AllNOSBProposalsDiscApr2017.pdf

USEPA. 2010. "Bisphenol A Action Plan." U.S. Environmental Protection Agency. March 29, 2010. 22 pp. https://www.epa.gov/sites/production/files/2015-09/documents/bpa_action_plan.pdf

USFDA. 2008a. "Draft Assessment of Bisphenol A for Use in Food Contact Applications." U.S. Food and Drug Administration, Washington, DC. August 14, 2008. 105 pp. https://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-0038b1_01_02_FDA%20BPA%20Draft%20Assessment.pdf

USFDA. 2008b. "Scientific Peer-Review of the Draft Assessment of Bisphenol A for Use in Food Contact Applications." FDA Science Board Subcommittee on Bisphenol A. October 31, 2008. 17 pp. https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4386b1-05.pdf

USFDA. 2010. "Update on Bisphenol A for Use in Food Contact Applications," U.S. Food and Drug Administration. January 2010. Available: http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM197778.pdf

USFDA. 2011. Updated Review of the Low-Dose Literature (Data) on Bisphenol A (CAS RN 80-05-7) and Response to Charge Questions Regarding the Risk Assessment on Bisphenol A." May 24, 2011. 119 pp. https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424074.pdf

USFDA. 2011a. "List of Indirect Additives used in Food Contact Surfaces." U.S. Food and Drug Administration. November 2011. https://www.fda.gov/food/ingredientspackaginglabeling/packagingfcs/indirectadditives/default.htm

USFDA. 2012a. "2012 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7)." U.S. Food and Drug Administration. August 22, 2013. 57 pp. https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424073.pdf

USFDA. 2012b. "21 CFR Part 177. Indirect Food Additives: Polymers." *Fed. Register* 77(137): 41899-41902. July 17, 2012.

USFDA. 2013. "21CFR Part 175. Indirect Food Additives: Adhesives and Components of Coatings." *Fed. Register* 78(134): 41840-41843. July 12, 2013.

USFDA. 2014a. "2014 Updated Review of Literature and Data on Bisphenol A (CAS RN 80-05-7)." U.S. Food and Drug Administration. June 6, 2014. 219 pp. https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424071.pdf

USFDA. 2014b. "Final Report for the Review of Literature and Data on BPA." U.S. Food and Drug Administration. June 6, 2014. https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/UCM424011.pdf

USFDA. 2017. "Bisphenol A (BPA): Use in Food Contact Applications." https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm064437.htm

Vandenberg, L.N., R. Hauser, M. Marcus et al. "Human Exposure to Bisphenol A (BPA)." *Reproductive Toxicol.* 24, (2007): 139-177.

Vandenburg, L.N., M.V. Maffini, C. Sonnenschein et al. "Bisphenol A and the Great Divide: A Review of Controversies in the Field of Endocrine Disruption." *Endocrine Rev.* 30, No. 1, (2009): 75-95.

Vandenberg, L.N., I. Chahoud, J.J. Heindel et al. "Urinary, Circulating, and Tissue Biomonitoring Studies Indicate Widespread Exposure to Bisphenol A." *Environ. Health Perspect.* 118, (2010): 1055-1070.

Vandenberg, L.N., T. Colborn, T.B. Hayes et al. "Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses." *Endocrine Rev.* 33, (2012): 378-455.

Vandenberg, L.N., S. Ehrlich, S.M. Belcher et al. "Low Dose Effects of Bisphenol A." *Endocrine Disruptors* 1, no. 1, (2013a): e26490.

Vandenberg, L.N., T. Colborn, T.B. Hayes et al. "Regulatory Decisions on Endocrine Disrupting Chemicals Should be Based on the Principles of Endocrinology." *Reprod. Toxicol.* 38, (2013b): 1-15.

Vandenberg, L.N., P. Hunt, J.P. Meyers et al. "Human Exposures to Bisphenol A: Mismatches Between Data and Assumptions." *Rev. Environ. Health* 28, No. 1, (2013c): 37-58.

Vandenberg, L.N. "Non-Monotonic Dose Responses in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study." *Dose Response* 12, (2014a): 259-276.

Vandenberg, L.N. 2014b. "Low-Dose Effects of Hormones and Endocrine Disruptors." In: *Vitamins and Hormones*, pp. 129-165.

Vogel, S.A. "The Politics of Plastic: The Making and Unmaking of Bisphenol A Safety." *Amer. J. Pub. Health* 99, no. S3, (2009): S559-S565.

Volkel, W., T.Colnot, G.A. Csanady et al. "Metabolism and Kinetics of Bisphenol A in Humans at Low Doses Following Oral Administration." *Chem. Res. Toxicol.* 15, (2002): 1281-1287.

Volkel, W., N. Bittner and W. Dekant. "Quantitation of Bisphenol A and Bisphenol A Glucuronide in Biological Samples by High Performance Liquid Chromatography-Tandem Mass Spectroscopy." *Drug Metab. Disposition* 33, No. 11, (2005): 1748-1756.

Volkel, W., M. Kiranoglu and H. Fromme. "Determination of Free and Total Bisphenol A in Human Urine to Assess Daily Uptake as a Basis for a Valid Risk Assessment." *Toxicol. Letters* 179, (2008): 155-162.

Vom Saal, F.S., B.G. Timms, M.M. Montano et al. "Prostate Enlargement in Mice due to Fetal Exposure to Low Doses of Estradiol or Diethylstilbestrol and Opposite Effects at High Doses. *Proc. Natl. Acad. Sci. USA* 94, (1997): 2056-2061.

Vom Saal, F.S., P.S. Cooke, D.L. Buchanan et al. "A Physiologically Based Approach to the Study of Bisphenol A and other Estrogenic Chemicals on the Size of Reproductive Organs, Daily Sperm Production and Behavior." *Toxicol. Ind. Health* 14, No. 1/2, (1998): 239-260.

Vom Saal, F.S. and C. Hughes. "An Extensive New Literature Concerning Low Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment." *Environ. Health Perspect.* 113, (2005): 926-933.

1838 Vom Saal, F.S. and W.V. Welshons. 2006. "Large Effects from Small Exposures. II. The Importance of
1839 Positive Controls in Low-Dose Research on Bisphenol A." *Environ. Res.* 100, (2006): 50-76.
1840
1841 Vom Saal, F.S., B.T. Akingbemi, S.M. Belcher et al. "Chapel Hill Bisphenol Expert Panel Consensus
1842 Statement: Integration of Mechanisms, Effects in Animals and Potential to Impact Human Health
1843 at Current Levels of Exposure." *Reprod. Toxicol.* 24, No. 2, (2007): 131-138.
1844
1845 Wagner, M. and J. Oehlmann. "Endocrine Disruptors in Bottled Mineral Water: Total Estrogenic Burden
1846 and Migration from Plastic Bottles." *Environ. Sci. Pollut. Res.* 16, (2009): 278-286.
1847
1848 Weber, M., M. Weber and M. Kleine-Boymann. "Phenol." *Ullmann's Encyclopedia of Industrial Chemistry.*
1849 (Weinheim: Wiley-VCH, 2004), pp. 503-518.
1850
1851 Welshons, W.V., K.A. Thayer, B.M. Judy et al. "Large Effects from Small Exposures. I. Mechanisms for
1852 Endocrine-Disrupting Chemicals with Estrogenic Activity." *Environ. Health Perspect.* 111, (2003):
1853 994-1006.
1854
1855 Welshons, W.V., S.C. Nagel and F.S. vom Saal. "Large Effects from Small Exposures. III. Endocrine
1856 Mechanisms Mediating Effects of Bisphenol A at Levels of Human Exposure." *Endocrinol.* 147, No.
1857 6, (2006): S56-S69.
1858
1859 Wetherill, Y.B., B.T. Akingbemi, J. Kanno et al. "In vitro Molecular Mechanisms of Bisphenol Action."
1860 *Reprod. Toxicol.* 24, (2007): 178-198.
1861
1862 Willhite, C.C., G.L. Ball and C.J. McLellan. "Derivation of a Bisphenol A Oral Reference Dose (RfD) and
1863 Drinking-Water Equivalent Concentration." J. Toxicol. Environ. Health, Part B, 11, (2008): 69-146.
1864
1865 Xu, J., Y. Osuga, T. Yano et al. "Bisphenol A Induces Apoptosis and G2-to-M Arrest of Ovarian Granulosa
1866 Cells." *Biochem. Biophys. Res. Comm.* 292, (2002): 456-462.
1867
1868 Yang, C.Z., S.I. Yaniger, V.C. Jordan et al. "Most Plastic Products Release Estrogenic Chemicals: a Potential
1869 Health Problem that can be Solved." *Environ. Health Perspect.* 119, (2011): 989-996.
1870
1871 Yang, C.Z., W. Casey, M.A. Stoner et al. "A Robotic MCF7:WS8 Cell Proliferation Assay to Detect Agonist
1872 and Antagonist Estrogenic Activity." *Toxicol. Sci.* 137, No. 2, (2014): 335-349.
1873
1874 Ye, X., X. Zhou, R. Hennings et al. "Potential External Contamination with Bisphenol A and other
1875 Ubiquitous Organic Environmental Chemicals during Biomonitoring Analysis: an Elusive
1876 Laboratory Challenge." *Environ. Health Perspect.* 121, (2013): 283-286.
1877
1878 Zalko, D., A.M. Soto, L. Dolo et al. "Biotransformations of Bisphenol A in a Mammalian Model: Answers
1879 and New Questions Raised by Low-Dose Metabolic Fate Studies in Pregnant CD1 Mice." *Environ.*
1880 *Health Perspect.* 111, (2003): 309-319.
1881
1882 Zoeller, R.T., T.R. Brown, L.L. Doan et al. "Endocrine-Disrupting Chemicals and Public Health Protection: a
1883 Statement of Principles from the Endocrine Society." *Endocrinol.* 153, (2012): 4097-4110.