Kaolin Pectin

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Kaolin: hydrated aluminum silicate, Al_2O_3 * $2SiO_n$ * $2H_2O$
Pectin: high-methoxy pectin, low-methoxy pectin (non-amidated forms)

Other Names:
Kaolin pectin: (same name)
Kaolin: china clay, Argilla, bolus alba
Pectin: Amforol, citrus pectin, methoxyl pectin, methyl pectin, methyl pectinate

Trade Names:
Kaolin pectin: Donnagel-MB, K-P, Kao-Spen, Kaopectate, Kapectolin

CAS Numbers:
Kaolin: 1332-58-7
Pectin: 9000-69-5

Other Codes:
Kaolin: EC – 310-194-1
INS – 948
Pectin: EC – 232-553-0
INS – 440

Summary of Petitioned Use

A petition was submitted to the National Organic Standards Board (NOSB) for adding kaolin pectin to the National List of Allowed and Prohibited Substances under Title 7 of the Code of Federal Regulations Section 205.603. Currently, kaolin is listed as an allowed nonsynthetic, nonagricultural substance for use in organic handling; pectin is listed as an allowed nonorganically produced agricultural substance for use in organic handling; and kaolin pectin is listed as an allowed synthetic substance for use in organic livestock production. Both kaolin and pectin are considered generally recognized as safe (GRAS) and used as inert additives in food, cosmetics, drugs, and pesticides. This report addresses kaolin pectin as a substance for use in organic livestock production. Kaolin pectin, formulated as a mixture of kaolin and pectin, combines the bacteria-adsorbing and antidiarrheal properties of kaolin with the gut-protecting properties of pectin. Kaolin pectin is used for both humans and animals.

Characterization of Petitioned Substance

Composition of the Substance:
Kaolin pectin is a formulated mixture of kaolin and pectin. It is medically used to treat diarrhea in both humans and livestock. The amount of pectin relative to kaolin varies and depends on the given commercial formulation. Typical kaolin-to-pectin ratios in commercial products range from 45:1 to 8:1. Understanding the kaolin pectin composition requires a fundamental understanding of its individual constituents—kaolin and pectin.

Kaolin is a natural hydrated aluminum silicate clay composed of approximately 47% silica (SiO_2), 40% alumina (Al_2O_3), and 13% water. Kaolin is a derivative of kaolinite, a mineral that comes from the Earth's crust (BASF 2021, KA 2018). Primary residual deposits of kaolinite are formed by the weathering or low-temperature hydrothermal alteration of feldspars, muscovite, and other Al-rich silicates prevalent in acid rocks, such as granites, rhyolites, and quartz diorites. Secondary deposits of kaolinite are observed in deltaic, lagoonal, or other non-marine environments to which its parent minerals have been transported under suitable non-alkaline conditions (Deer et al. 2013). Kaolinite and its derivatives are known to contain 1:1 uncharged dioctahedral layers with silica tetrahedral and alumina octahedral sheets (Abdullahi et al. 2017). A depiction of its chemical structure is provided in Figure 1 (Kotal et al. 2015).

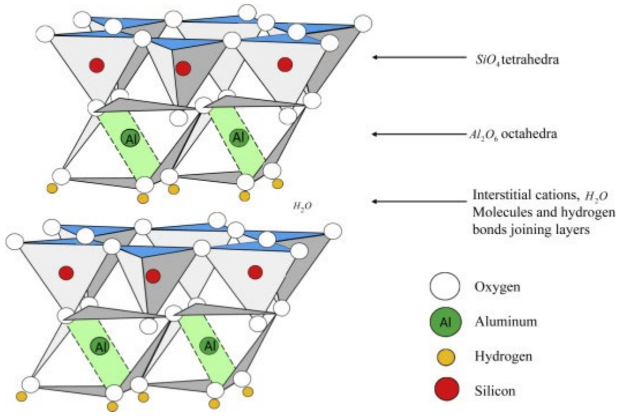

Figure 1. Crystal structure of kaolin

Kaolin is typically used as a gelling agent, thickening agent, or stabilizer in a variety of commercial products. In terms of medical use, kaolin is believed to act as an antidiarrheal due to its ability to adsorb large numbers of bacteria and toxins and reduce water loss.

Pectin is a high molecular weight, linear polysaccharide that consists mainly of galacturonic acid and galacturonic acid methyl ester units. The main chain of galacturonic acid is often interrupted by rhamnose, which causes deviations of the main chain. The main chain is also interrupted by short branches of neutral sugars such as xylose, galactose, and arabinose (CYC 2021). Average molecular weights for pectin range from about 50,000 atomic mass units (amu) to 150,000 amu. A depiction of the chemical structure of the main D-galacturonic acid unit that makes up pectin is provided in Figure 2.

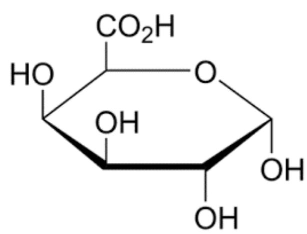

Figure 2. Chemical structure of D-galacturonic acid

Pectin is typically classified by its degree of esterification. In high methyl ester or HM-pectin, greater than 50% of the carboxyl groups occur as methyl esters, while the remaining carboxylic acid groups are either in the free acid or salt form (sodium, potassium, or ammonium). When less than 50% of the carboxyl groups occur as a methyl ester group, pectins are referred to as low methyl ester or LM-pectin. A depiction of a 5-unit HM-pectin oligomer chain is provided in Figure 3.

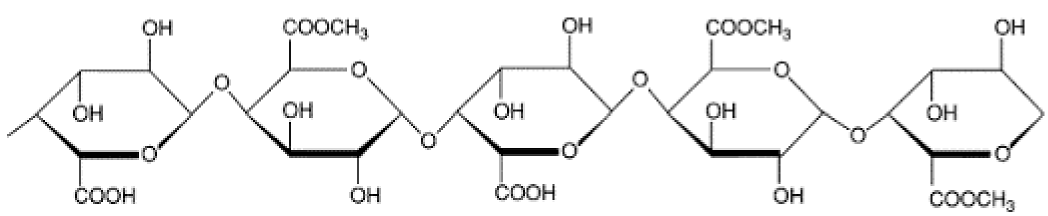

Figure 3. Chemical structure of HM-pectin containing both free acid and methyl ester substitutions

Here, 60% or 3 out of the 5 individual sugar units contain methyl ester groups, while 2 of the 5 units contain carboxylic acid groups. Yet another form of pectin, known as amidated pectin, may be obtained from high ester pectin when ammonia is used to convert the carboxylic groups into acid amide groups. Regardless of pectin classification, the individual galacturonic acid units that make up pectin are linked by 1,4 glycosidic linkages.

Pectin is present in almost all plants' cell walls and provides structural integrity for plants. Pectins differ by their chemical configuration, neutral sugar content, and molecular weight (Flutto 2003). Due to its presence in all landbased plants, pectin has been part of the human diet for thousands of years. Pectin has been evaluated and cleared by JECFA (the Joint FAO/WHO Expert Committee on Food Additives) for use in foods and is deemed to be a valuable and harmless food additive.

Source or Origin of the Substance:

Kaolin is a natural hydrated aluminum silicate clay that is derived from kaolinite, a mineral that comes from the Earth's crust (KA 2018). Primary residual deposits of kaolinite are formed by the weathering or low-temperature hydrothermal alteration of feldspars, muscovite, and other Al-rich silicates prevalent in acid rocks, such as granites, rhyolites, and quartz diorites. Secondary deposits of kaolinite are observed in deltaic, lagoonal, or other non-marine environments to which its parent minerals have been transported under suitable non-alkaline conditions (Deer et al. 2013). The clay is mined and subsequently calcined in a kiln to form a fine powder. The fine powder consists of platelet-shaped particles with a large surface area, providing pronounced adsorptive properties.

Pectins are also natural and mainly derived from citrus fruits and apples. Citrus pectins are largely derived from the peel of lemon and lime and, to a lesser extent, orange and grapefruit peel. Citrus peel is a by-product from juice and oil pressing manufacturing processes. Apples also provide a source of pectin. Apple pomace is the residue from apple juice production and is the raw material for commercial apple pectins. Apple pectins are darker in color when compared to citrus pectins but provide similar properties.

Properties of the Substance:

Kaolin is an odorless, white to yellowish or grayish powder that is insoluble in water, ether, dilute acids, and alkali hydroxides. When wet, it darkens and develops an earthy odor (Lewis 2007, NOAA 2021, NIOSH 2019). This substance's pH can range from 4.0 to 5.0, which places it in the acidic range (HSDB 1983).

Pectin is an odorless, white to light brown powder that is soluble in pure water. The solubility of pectins in water is dependent on many factors, including the degree of methylation, molecular weight, counterions present in the solution, temperature, and pH (Gawkowska et al. 2018). As previously stated, different pectin molecules have various degrees of methylation (DM). HM-pectins have a DM>50%, and LM-pectins have a DM<50%. The degree of methylation generally impacts its solubility. HM-pectins typically dissolve in water when the solid contents are less than 20%. Dissolution of HM-pectins above the 20% solids threshold becomes increasingly difficult. Of particular note is that pectins will not dissolve in a medium where gelling conditions already exist.

The degree of methylation (DM) also plays a role in pectin gel formation and the gelling mechanism. In general, a high degree of methylation favors gelling. HM-pectins tend to form gels through stacking of esterified smooth regions. Junctions are stabilized by hydrogen bonds, and gelling only occurs in acidic environments (CYC 2021). Conversely, LM-pectins gel via the formation of complexes with Ca^{2+}. The association of non-esterified, hydrophilic regions within the pectin forms hydrophilic regions which attract calcium cations. LM-pectins are commercially used for their ability to form a spreadable gel in the presence of a dehydrating agent or calcium ion. Pectins are stable when at room temperature and at a pH of 5.0 to 6.0, where they exist as reversible colloids (Smith 2003). As temperature increases, pH increases because pectin chains cleave by a beta-elimination reaction (BeMiller 1986).

The properties of kaolin and pectin are summarized in Table 1.

Table 1. Properties of kaolin and pectin

Properties	Kaolin	Pectin
CAS No.	1332-58-7	9000-69-5
Molecular Formula	$Al_2O_3 * 2SiO_n * 2H_2O$	Varies
Molecular Weight	258.16 g/mol	Varies, 50,000 to 150,000

Appearance	White to yellowish or grayish powder	White to light brown powder
Melting Point	1750 °C	142–144 °C
Density	2.6 g/mL	Varies
pH	4.0–5.0	5.0–6.0
Solubility	Insoluble in water, ether, dilute acids, and alkali hydroxide	Soluble in water; Insoluble in aqueous-based solutions where gelling is already present

SOURCES: HSDB 1983, MS 2021, PC 2012, PC 2005

With regard to the combination of kaolin with pectin, there have been a variety of studies that have explored their interaction and subsequent impact on physical characteristics. The degree of kaolin flocculation and the gelling properties of pectin are among the primary parameters that have been explored. In general, organic matter tends to adsorb to the surface of clay particles (such as kaolin) through hydrogen bonding, typically prompting flocculation of the clay. However, Wang et al. (2020) demonstrated that the addition of pectin to a kaolin suspension slowed down the flocculation of kaolin. They demonstrated that after pectin was dissolved in water, the amino functional groups along the pectin chain became weakly ionized, subsequently generating hydroxide ions in solution. These ions further reduced the zeta potential in the aqueous system which contributed to the reduction in flocculation. Muszynski et al. (2017) explored the impact on gelling characteristics when mixing kaolin with pectin. They demonstrated that the addition of kaolin to LM-pectin resulted in an increase in hardness, adhesiveness, and flexibility of the kaolin-enriched gels.

<u>Specific Uses of the Substance:</u>
This petition concerns the use of kaolin pectin in the medical treatment of livestock. Kaolin pectin is used as an adsorbent to treat mild to moderate cases of acute diarrhea and as a gut protectant for both humans and livestock.

Kaolin alone has been tested on calves, lambs, and kids, according to older studies, but these studies reported a lack of evidence of benefit for the treatment of diarrhea in tested animals (Khan 2005, Rivera et al. 1978). Kaolin without pectin is used with other compounds in medications such as Kaocasil and Kao-lumin.

Pectins are used as emulsifiers, gelling agents, thickeners, and stabilizers in a wide variety of food products. Traditionally pectin has been used in jams, fruit jellies, and a variety of sugar products. It was found that pectin provided the desired texture, limited the creation of water/juice on top, and promoted the even distribution of fruit within a given product. Pectins are also found in pharmaceuticals and cosmetics. In cosmetics, they are used for binding, emulsion stabilization, and viscosity control (Sebe et al. 2012).

<u>Approved Legal Uses of the Substance:</u>
Kaolin pectin was approved by the U.S. Food and Drug Administration (FDA) as a synthetic substance allowed for use in organic livestock production (7 CFR § 205.603(a)(17)). Specifically, kaolin pectin is approved for use as an adsorbent, antidiarrheal, and gut protectant.

Kaolin pectin, as a combination, is not listed by the FDA as generally recognized as safe (GRAS). However, kaolin and pectin are individually considered as GRAS. The GRAS conditions (21 CFR 186.1256) for kaolin are the following:

1. Use in the manufacturing of paper and paperboard that have contact with food
2. Use at levels not to exceed current good manufacturing practice

Additionally, kaolin was approved by the FDA as a nonagricultural (nonorganic) substance allowed as an ingredient in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))" (7 CFR § 205.605(a)). Kaolin is also approved for use in anorectal drugs for over-the-counter human use (21 CFR 346.14(a)(5)).

Under the U.S. FDA CFR, the non-amidated form of low methyl pectin is a GRAS ingredient in food. The GRAS conditions for pectins (CFR Title 21 §184.1588(a)) are the following:

1. Use as emulsifiers, stabilizers, and thickeners
2. Use in food at levels not to exceed current good manufacturing practice

Pectin was also approved by the FDA as a nonorganically produced agricultural product allowed as an ingredient in or on processed products labeled as "organic" (7 CFR §205.606(p)).

The United States Environmental Protection Agency lists both kaolin and pectin separately as inert ingredients in pesticides (40 CFR 152.25: Exemptions for pesticides of a character not requiring Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) regulation—Inert Ingredients).

Action of the Substance:

Kaolin pectin is currently allowed for use as an adsorbent, an antidiarrheal, and a gut protectant in livestock. Specifically, kaolin and pectin are administered together orally to serve as an adsorbent and protectant, respectively. Kaolin is a natural hydrated aluminum silicate that is believed to counter diarrhea by adsorbing large numbers of bacteria and toxins and reducing water loss. Due to its large surface area, platelet shape, and crystal structure, kaolin has been shown to be medically beneficial for the adsorption of lipids, proteins, bacteria, and viruses (William and Haydel 2010). In contrast, pectin is a polyuronic polymer which is used to protect the gut. Pectin is believed to mitigate inflammation by coating the intestines. Pectin has been described as a prebiotic and promotes the growth activity of beneficial bacteria while inhibiting the growth of harmful bacteria in the gastrointestinal tract (Krath et al. 2010). Overall, studies have not shown that kaolin pectin yields a decrease in stool frequency or fecal weight and water content even though stools appeared more formed. Both kaolin and pectin are not adsorbed following oral administration, as up to 90% of pectin is decomposed in the gastrointestinal tract (Holloway et al. 1983). For chronic diarrhea, use is recommended temporarily until the etiology is determined. Kaolin with pectin should not be used if diarrhea is accompanied by fever or if there is blood or mucus in the stool. Kaolin and pectin are combined in various concentrations in commercially available preparations, with kaolin-to-pectin ratios ranging from 45:1 to 8:1. Kaolin pectin may also be combined with vitamin A to treat bacterial diarrhea in calves.

Combinations of the Substance:

Kaolin pectin formulations for both human and animal use may include a variety of inactive ingredients, including stabilizers, preservatives, flavoring, and colorants. Methyl para-hydroxybenzoate and sorbic acid are among the preservatives that are commonly used with kaolin pectin.

In terms of its impact on the efficacy of other medications, kaolin pectin may lower the bioavailability of other ingested medications. For example, kaolin pectin was found to decrease the beneficial effects of other orally administered drugs such as deferasirox and penicillamine (Gaynor and Muir 2009). The presence of aluminum in kaolin was found to impair the adsorption of other drugs, such as oral lincomycin, erythromycin, and digoxin (EDI 1978, McEvoy 1987). Overall, kaolin has adsorption-related interactions with many drugs, including but not limited to allopurinol, Lincorex, Pentazine, Serentil, trifluoperazine, and Vesprin (DR 2021). For these reasons, kaolin pectin formulations should be used at least three hours before or after any other medications to ensure excretion and avoid interactions (Pray 2006).

Status

Historic Use:

Kaolin pectin is primarily known for its use in treating diarrhea in both humans and animals, including cattle and horses, calves and foals, and dogs and cats. Kaolin pectin may also be used in conjunction with 15 mL sucralfate suspension containing diphenhydramine syrup to treat a sore mouth (oral mucositis) caused by radiation treatment.

Individually, kaolin is an essential ingredient in the manufacturing of china, porcelain, paper, rubber, paint, and many other products. Kaolin is also used in cosmetics to cleanse and exfoliate the skin, as well as add absorbency, texture, and bulk to products. It is commonly found in face powders, face masks, creams and lotions for oily skin, bath powders, foundation, powdered blush, deodorants, and soaps. In terms of medical use, kaolin has been explored as an antidiarrheal; as a hemostatic agent for activating coagulation, reducing inflammation in the colon; and for ulcers (Dalbert et al. 2006). Kaolin has also been explored as an antacid (Linares and Rosa-Brussin 2004) and used as an insecticide for a variety of arthropods (Barker et al. 2007, Barker et al. 2006, Sackett et al. 2005).

Individually, pectin is used as an emulsifier, a gelling agent, a thickener, and a stabilizer in a variety of food products. It is used in the preparation of jellies, jams, desserts, dairy products, yogurts, and beverages. Additionally, pectin is used as an additive in nutritional and health products and is also used as an excipient in pharmaceutical and medical applications. A recent review of the nutritional benefits of pectin consumption detailed the prebiotic attributes of pectin (Lara-Espinoza et al. 2018). For example, the consumption of pectin was found to increase beneficial microbial populations in the gastrointestinal tract. Pectin also exhibited several beneficial gastrointestinal physiological effects, including the delay of gastrointestinal emptying, decreasing the time of gastrointestinal transit, reducing glucose absorption, and increasing fecal mass. The intestinal fermentation of pectin yielded acetate, propionate, and butyrate, all of which play a key role in the prevention and treatment of metabolic syndrome, intestinal disorders, and cancer—a positive effect in the treatment of ulcerative colitis, Crohn's disease, high blood pressure, diarrhea, and obesity.

Organic Foods Production Act, USDA Final Rule:

According to the Organic Foods Production Act of 1990, no medication should be administered to livestock, other than vaccinations, in the absence of illness for farms to be certified as organic. Kaolin pectin is listed in USDA 7 CFR §205.603(a) under synthetic substances allowed for use in organic livestock production as an adsorbent, an antidiarrheal, and a gut protectant only when medically necessary. Kaolin itself is listed in CFR §205.605(a) as a nonsynthetic, nonagricultural (nonorganic) substance that is allowed as an ingredient in or on processed products labeled as "organic." Pectin, in non-amidated forms, is listed in §205.606(p) as a nonorganically produced agricultural product that is allowed as an ingredient in or on processed products labeled as "organic."

Code of Federal Regulations (CFR) Title 21

The FDA has declared both kaolin and pectin as generally recognized as safe (GRAS), in Title 21 §186.1256 and §184.1588, respectively (CFR 2020b).

International

Canada, Canadian General Standards Board—CAN/CGSB-32.311-2020, Organic Production Systems Permitted Substances List

Kaolin pectin is not on the Organic Production Systems Permitted Substance List. Kaolin clay is listed in Table 4.2 as a substance for crop production, specifically as a production aid. It is cleared to be used in its calcinated form and can only be processed or fortified with substances that are listed in Table 4.2 as a production aid. Kaolin is listed in Table 6.5 as a processing aid for use as a clarifying agent. Pectin is listed in Table 6.3 as an ingredient classified as a food additive.

CODEX Alimentarius Commission—Guidelines for the Production, Processing, Labelling, and Marketing of Organically Produced Foods (GL 32-1999)

Kaolin pectin is not listed in the CODEX Guidelines. Kaolin is listed in Table 4 as a processing aid that can be used for the preparation of products of agricultural origin with no limitations. It is also listed as a processing aid for bees and livestock products, to be used for the extraction of propolis. Pectins are listed in Table 3 for ingredients of nonagricultural origin as a food additive, with no specific conditions. It is also listed as an item for processing livestock and bee products, specifically milk products, only in its unmodified form.

European Economic Community (EEC) Council Regulation—EC No. 834/2007 and 889/2008
Kaolin pectin is not listed in the EEC Regulation. Kaolin clays are listed in Table 1.3 as technological additives that act as a binder and anti-caking agent. Kaolin is in Annex VIII, Section B, as a processing aid that may be used for processing ingredients of agricultural origin from organic production. It is authorized to be used for preparation of foodstuffs of plant and animal origin. Its specific conditions include its use for propolis, and it must be in compliance with specific purity criteria for food additives according to the EEC. Pectin is listed in Annex VIII, Section A, as a food additive to be used in milk-based products. It is authorized to be used in preparation of foodstuffs of plant and animal origin.

Japan Agricultural Organic Standard (JAS)
Kaolin pectin is not listed in the JAS. Kaolin is listed in the JAS for Organic Processed Foods where it is limited for use in processed foods of plant origin. Pectin is also listed in the JAS for Organic Processed Foods where it is limited for use in dairy products.

International Federation of Organic Agriculture Movements (IFOAM)
Kaolin pectin is not listed by IFOAM. Kaolin can be found in Appendix 4, Table 1, as an approved processing/post-harvest handling aid with no limitations. Pectin is listed in the same table as an approved additive, and the limitation is that it must be unmodified.

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: Indicate which category in OFPA the substance falls under: (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the Environmental Protection Agency EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4 but is exempt from a requirement of a tolerance, per 40 CFR part 180?

Kaolin pectin contains active ingredients that fall into the livestock medicines category and the production aids category. Both kaolin and pectin appear on the EPA's list of inert materials (List 4) and are exempt from a requirement of tolerance. Pectin is categorized by the EPA as a commodity inert product for non-food use.

Evaluation Question #2: 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)).

Kaolin is a natural clay that is formed from weathered granite that was previously below the Earth's crust (KA 2018). Primary residual deposits of kaolinite are formed by the weathering or low-temperature hydrothermal alteration of feldspars, muscovite, and other Al-rich silicates prevalent in acid rocks, such as granites, rhyolites, and quartz diorites. Secondary deposits of kaolinite are observed in deltaic, lagoonal, or other non-marine environments to which its parent minerals have been transported under suitable non-alkaline conditions (Deer et al. 2013). During its processing, the clay is mined and washed to clear away sand and impurities. Kaolin does not have any known chemical interactions during its processing (DR 2021). The washed clay is subsequently calcined in a kiln to form a fine powder.

Pectins are isolated from various plants, the most common being apples, citrus fruits, and beet pulp (CFR 2020a, Smith 2003, Windholz 1983). Citrus pectins are largely derived from the peel of lemon and lime and, to a lesser extent, orange and grapefruit peel. Citrus peel is a by-product from juice and oil pressing manufacture processes. Apples also provide a source of pectin. Apple pomace is the residue from apple juice production and is the raw material for commercial apple pectins. Apple pectins are darker in color when compared to citrus pectins but provide similar properties.

The pectin manufacturing process may be broken down into 4 main steps: (1) Pectin is first extracted from the raw material using hot acidified water. Hydrochloric acid, nitric acid, sulfuric acid, or organic-based acids such as citric acid or tartaric acid may be used in this process (Maric et al. 2018). Note, depending on the pH of this wash, hydrolysis of 1,4 glycosidic bonds along the chain may occur, leading to a certain degree of depolymerization. (2) Next, the extract is purified and concentrated via centrifugation and filtration steps. (3) Isolation of the pectin from the solution is achieved by precipitating a concentrated pectin solution with either an alcohol (ethanol, methanol, isopropanol) or an aluminum salt. If an aluminum salt is used, aluminum pectinate forms and is subsequently converted to the free acid form using acidified alcohol followed by neutralization with a slightly alkaline alcohol rinse. The resultant pectin is classified as a HM-pectin. (4) In order to convert HM-pectin to LM-pectin, the HM-pectin is demethylated under either acidic or basic conditions. Ammonia can also be used for this demethylation step for the formation of LM-pectin, yielding an amidated form of LM-pectin. Finally, HM-pectin may also be demethylated using an enzyme called pectin methylesterase (PME). PME has various sources in nature, and each PME has different modes of action. PME from fungi randomly demethylates the pectin main chain, while PME from higher plants demethylate the main chain in a block-wise manner. The advantage of the PME approach is that it enables demethylation without hydrolysis of the pectin main chain and without the use of an alkaline solution (Hotchkiss et al. 2002).

A description of how kaolin is physically mixed with pectin commercially is not provided in the literature. However, inspection of commercially available kaolin pectin products on the market reveals that typical formulations are in the liquid suspension form and include the active ingredients kaolin and pectin and inactive ingredients such as purified water, xanthan gum, artificial flavors, methyl paraben, artificial color, propyl paraben, and sodium saccharin.

<u>Evaluation Question #3:</u> 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)).

Classification of a given manufacturing process as either chemical or biological will be separately described for kaolin and pectin. First, kaolin is a naturally occurring clay that is formed from weathered granite. Kaolin is derived from feldspar, which is a rock-forming mineral that makes up about 41% of the weight of the Earth's crust. As kaolin weathers, it significantly decomposes and is easily broken down into smaller pieces. For commercial use, kaolin is washed with water after collection to remove impurities and subsequently calcined to form a fine kaolin powder consisting of platelet-shaped particles. Since the processing of kaolin involves the heating of non-biological matter, as per the NOP guideline on the classification of materials (NOP-5033 4.8), kaolin is categorized as a synthetic material derived from a chemical process.

Pectins are created naturally via biological processes in plants during the early stages of primary cell wall growth. Specifically, HM-pectins are synthesized by plants. HM-pectins used in commercial use are often extracted from citrus peel (primarily lemon and lime). These citrus-based HM-pectins are a by-product of juice and oil pressing manufacturing processes. In order to extract HM-pectin, the citrus peel raw material is isolated using solvent extraction with hot acidified water. Next, the extract is purified and concentrated via centrifugation and filtration steps. Isolation of the pectin from this purified solution is achieved by precipitating the concentrated pectin solution with ethanol. The mixture is then mixed until the pectins float to the top (Venkatanagaraju et al. 2019, Voragen et al. 2009). The overall extraction and isolation steps for obtaining HM-pectins described above are non-chemical in nature. As per NOP guidelines on material extraction (NOP 5033 4.6), a material is still considered to be a natural material if the following extraction criteria are met:

- At the end of the extraction process, the material has not been transformed into a different substance via chemical change;
- The material has not been altered into a form that does not occur in nature; and

- Any synthetic materials used to separate, isolate, or extract the substance have been removed from the final substance (e.g., via evaporation, distillation, precipitation, or other means) such that they have no technical or functional effect in the final product

Based on this criteria, HM-pectins are described and classified as a natural material.

Due to its optimal gelling properties in food and medical applications, LM-pectins are often preferred over HM-pectins. To convert HM-pectin to the desired LM-pectin form, the HM-pectin is demethylated using 1 of 4 approaches. These include the use of acids, alkalis, enzymes, or ammonia in alcohol. Acid demethylation is commonly used to manufacture LM-pectin. Hydrochloric acid, nitric acid, sulfuric acid, or organic-based acids such as citric acid or tartaric acid may be used in this process (Maric et al. 2018). The ammonia in alcohol approach yields amidated forms of LM-pectin. Pectin is classified as a nonorganically produced agricultural product allowed as an ingredient in or on processed products labeled as "organic" (7 CFR § 205.606).

Evaluation Question #4: Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518(m)(2)).

Kaolin pectin does not have any by-products. As a natural component of soil, kaolin is a product of the uppermost part of the Earth's crust, which has a depth of ~1.5 km and is 75% sedimentary rock. The presence of kaolin is widespread and mainly found in sedimentary rock. The 4 main environments in which kaolin is present are vein-type deposits, volcanic and pyroclastic deposits, skarn to epithermal deposits, and granitic rocks and their affiliates (Dill 2016). Pectins are naturally occurring polysaccharides found in the cell wall of numerous plants. Hence, the presence of pectin is observed throughout nature and ubiquitous in the world's vegetation.

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518(m)(2)).

Kaolin pectin has no known toxicological effects and has been deemed "practically non-toxic" (Gosselin et al. 1984). There are respirable exposure limits on kaolin set by the U.S. Department of Labor's Occupational Safety and Health Administration (OSHA). OSHA states that kaolin's permissible exposure limit is 15 mg/m^3. The short-term inhalation of kaolin dust can cause lung irritation, while long-term inhalation can cause fibrosis and impaired lung function (Rom 1992). In terms of ingestion, the lethal oral dose for humans is more than 2.2 pounds for a 150-pound person (Gosselin et al. 1984). Similarly, pectins do not exhibit any toxicity effects to humans or the environment. In one study, the impact of pectin consumption on weight gain in rats was explored (Takagi et al. 1997). It was concluded from this study that the consumption of pectin in water concentrations of 0.5% (by mass) or greater yielded weight gain in the rats. Additionally, no negative toxicological effects were observed.

Evaluation Question #6: Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518(m)(3)).

Manufacture

Extensive safety and toxicological data exist on the impact of kaolin and pectin on human health and the environment. Reviews by JEFCA (the Joint FAO/WHO Expert Committee on Food Additives) and the U.S. FDA suggest that the petitioned substance is not harmful to human health or the environment.

Kaolin is a mined resource, and thus, inhalation by humans is a concern. Proper safety mitigation measures such as mask wearing should be employed in the manufacturing environment. Kaolin is also a natural component of soil and occurs widely in ambient air as floating dust. Accordingly, the exposure of the general population to this material is prevalent globally, albeit at low concentrations. In the vicinity of mines and industrial projects, kaolinite is likely to be present at higher concentrations in air (Adamis et al.

2005). With regard to the impact of calcination on kaolin composition, M'anyai et al. (1970) determined the impact of temperature on kaolin decomposition. Complete dehydration of kaolin resulted in the formation of metakaolinite between the temperatures 500°C to 650°C. Heating to higher temperatures, 800°C and 950°C, was found to result in the formation of γ -Al_2O_3 (mullite) or SiO_2 (cristobalite).

With regard to environmental impact of pectin processing, the extraction of HM-pectin and subsequent conversion to LM-pectin involves simple solvent extraction and conversion methods using dilute acids and common solvents such as methanol or ethanol. Thus the process to make LM-pectin is largely benign, and waste solvents may be either disposed of or neutralized. Overall, pectin is a by-product of the fruit juice industry, and its production serves to reduce the waste streams generated by these processes.

Use

Kaolin and pectin are categorized as generally recognized as safe (GRAS) by the U.S. Food and Drug Administration when used as intended, and side effects rarely occur. In terms of its impact on the efficacy of other medications, kaolin pectin may lower the bioavailability of other ingested medications. For these reasons, kaolin pectin formulations should be used at least 3 hours before or after any other medications to ensure excretion and avoid interactions.

Disposal

For accidental releases of pectin, its Material Safety Data Sheet (MSDS) indicates that environmental precautions are not applicable. Both kaolin and pectin are not believed to be dangerous to the environment with respect to mobility, persistency, degradability, bio-accumulative potential, aquatic toxicity, and other data relating to the ecotoxicity. Small quantities of waste are disposed of as domestic refuse. Greater quantities are disposed of in accordance with local regulations.

<u>Evaluation Question #7</u>: Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518(m)(1)).

There is no evidence that kaolin pectin for use as medicine in livestock would cause harmful interactions in organic crop, livestock production, or livestock handling. Because kaolin is made up of natural components, the fecal excretion of kaolin will not cause harm. Most of the pectin consumed by animals is degraded in the intestine.

When used in combination with other medications, kaolin pectin may lower the bioavailability of other ingested medications in livestock. For example, kaolin pectin was found to decrease the beneficial effects of other orally administered drugs such as deferasirox and penicillamine (Gaynor and Muir 2009). The presence of aluminum in kaolin was found to impair the adsorption of other drugs such as oral lincomycin, erythromycin, and digoxin (EDI 1978, McEvoy 1987). Kaolin has also been shown to exhibit adsorption-related interactions with other drugs, including but not limited to allopurinol, Lincorex, Pentazine, Serentil, trifluoperazine, and Vesprin (DR 2021). For these reasons, kaolin pectin formulations should be used at least 3 hours before or after any other medications to ensure excretion and avoid interactions (Pray 2006).

<u>Evaluation Question #8:</u> Describe any effects of the petitioned substance on biological or chemical interactions in the agroecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518(m)(5)).

There are no reports on the impact of kaolin pectin on biological or chemical interactions within the agroecosystem. Kaolin by itself is already present in many soil samples throughout the world. Pectin by itself has been explored as an additive or fertilizer in soil and was shown to enhance the growth of beneficial bacteria, which in turn aids in root, nodule, and plant development (Hassan et al. 2019).

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

There is no evidence that kaolin pectin may be harmful to the environment. Both kaolin and pectin are naturally produced and ubiquitous in the environment.

<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)).

Occupational exposure to kaolin dust has caused fibrosis and pneumoconiosis in miners and kaolin processors. This pulmonary damage was linked to the direct inhalation of clay dusts (Elmore 2002). The short-term inhalation of kaolin dust can cause lung irritation, while long-term inhalation can cause fibrosis and impaired lung function (Rom 1992). Hence, the U.S. Department of Labor's Occupational Safety and Health Administration (OSHA) has set the respirable exposure limit for kaolin to be 15 mg/m^3.

With respect to pectin, The Journal of Allergy Asthma Immunology detailed a clinical case of pectin anaphylaxis (Ferdman et al. 2006). A possible association with cashew allergy was also reported. Doctors were able to identify a child with pectin-induced food anaphylaxis after ingesting a fruit smoothie containing pectin of citrus origin. The anaphylaxis to pectin and cashews was confirmed by skin tests or radioallergosorbent tests.

<u>Evaluation Question #11:</u> Describe all natural (nonsynthetic) 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)).

Bismuth subsalicylate serves a similar purpose to kaolin pectin for the treatment of diarrhea in conventional livestock. Zeolites and bentonites are natural clays that may also be used as effective adsorbents of toxic agents, particularly aflatoxins (Parlat et al. 1999, Phillips 1999, Oguz and Kurtoglu 2000, Ortatatli and Oguz 2001, Rizzi et al. 2003). These zeolites and bentonites are primarily used as additives to livestock feed—that is, for the prevention of sickness as opposed to the treatment of diarrhea. They effectively minimize adverse effects of aflatoxins on feed intake, thereby enhancing performance and nutrient conversion.

<u>Evaluation Question #12:</u> Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518(m)(6)).

A livestock production operation must establish and maintain preventive animal health care practices. This operation must establish appropriate housing, pasture conditions, and sanitation practices for the livestock to minimize the occurrence and spread of diseases and parasites. The operation must establish a feed ration that includes vitamins, minerals, proteins and/or amino acids, fatty acids, energy sources, and fiber. Additionally, the operation must administer vaccines and other veterinary biologics to prevent sickness. When these preventive practices are inadequate to prevent sickness, the producers may administer the allowed medications included on the National List of Allowed and Prohibited Substances for use in livestock operation.

Report Authorship

The following individuals were involved in research, data collection, writing, editing, and/or final approval of this report:

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