Xanthan Gum

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Xanthan gum

Other Names:
Xanthan
Corn sugar gum
Gummi xanthanum
Gum xanthan

Trade Names:
Keltrol®
Satiaxane®
GRINDSTED® Xanthan
NovaXan™
Ticaxan®
Ziboxan®

CAS Number:
11138-66-2

Other Codes:
EINECS No. 234-394-2
E415
INS 415

Summary of Petitioned Use

Xanthan gum is currently included on the National List of Allowed and Prohibited Substances (hereafter referred to as the National List) as a nonagricultural (nonorganic), synthetic substance allowed as an ingredient in or on processed products labeled "organic" or "made with organic (specified ingredients or food group(s))" (7 CFR 205.605[b]). Xanthan gum is used in a variety of food items as a stabilizer, thickener, and emulsifier with texturizing attributes, typically at concentrations of 0.05% to 0.5% by weight of the processed food (García-Ochoa et al., 2000; Sworn, 2009; Jungbunzlauer, 2015; TIC Gums, Inc., 2015a).

Characterization of Petitioned Substance

Composition of the Substance:
Xanthan gum is a high-molecular-weight polysaccharide produced by pure-culture fermentation of a carbohydrate (e.g., glucose, sucrose) with the bacterium *Xanthomonas campestris* (García-Ochoa et al., 2000). The polysaccharide secreted by the bacterium is harvested by precipitation with an alcohol. It is usually manufactured as a sodium, potassium, or calcium salt that is readily soluble in water (EFSA, 2011; García-Ochoa et al., 2000). Xanthan gum is a hydrocolloid, a substance that disperses in water, providing a thickening or gelling effect by increasing the viscosity of a solution.

The general structure of xanthan gum (see Figure 1) consists of a cellulose backbone with trisaccharide side chains (Belitz et al., 2009). Repeated pentasaccharide units are formed by two molecules of glucose, two molecules of mannose (a carbohydrate), and one molecule of glucuronic acid (an oxidized glucose molecule). The glucose backbone is protected from chemical attack (e.g., from acids, alkalis, or food enzymes) by the large overlapping side chains each consisting of a glucuronic acid unit between two mannose units. When xanthan gum is dissolved in solution, the side chains wrap around the backbone, and it is thought that this contributes to the stability of xanthan gum under adverse conditions such as acidic and high salt environments (Sworn, 2009). The side chains carry a negative charge due to the presence of glucuronic acid and pyruvate groups that are neutralized by manufacturers using positively charged sodium, potassium, or calcium ions (see Figure 1)(Cargill, 2016b). A pyruvate group is a three-carbon biological molecule that plays an important role in biochemical pathways. The amount of pyruvate groups in commercial xanthan gum will vary depending on the fermentation conditions. This affects the viscosity of xanthan gum solutions because the presence of fewer pyruvate groups corresponds to a more viscous solution when stationary that is more free flowing when poured (Burdock, 2006).

Various bacteria in the *Xanthomonas* genus can be used to create xanthan gum although the resulting polysaccharide composition may vary slightly (García-Ochoa et al., 2000). Xanthan gum is a stiff, high-molecular-weight molecule that can aggregate, which makes exact molecular weight values difficult to obtain (Born, 2005). The xanthan gum molecule has been observed to have two conformations (i.e., molecular shapes): helix and random coil. When xanthan gum is in solid form, its molecular structure is a rigid helix. In solution, xanthan gum can undergo a conformational change during heating to a more flexible, disordered state at high temperatures (Sworn, 2011).

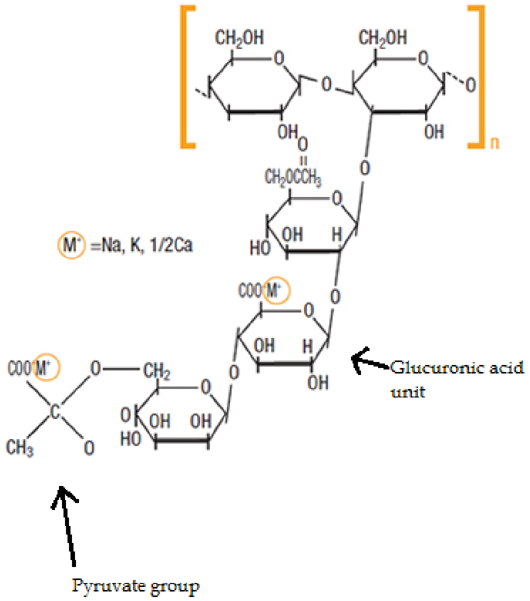

Figure 1: Molecular Structure of Xanthan Gum (Cargill, 2016b)

Source or Origin of the Substance:

Xanthan gum was discovered in the 1950s at the Northern Regional Research Laboratories of the United States Department of Agriculture (USDA), and its commercial production began in 1964 by Kelco Company (later to become CP Kelco). In the literature, xanthan gum is typically described as a natural, extracellular polysaccharide produced by most bacteria of the *Xanthomonas* genus as part of the capsule or outer covering of the cells (García-Ochoa et al., 2000). This extracellular polysaccharide is a secondary metabolite[1] of the bacteria, and it helps to prolong survival and increase resistance of the bacteria to temperature and ultraviolet (UV) light. Xanthan gum is the major component of the bacterial slime produced by *Xanthomonas* species (Born et al., 2005). The species used to commercially produce food-grade xanthan gum is *X. campestris*. It is an obligate aerobe, meaning that it requires oxygen for metabolism. It is a gram-negative, short, rod-shaped bacterium. Its colonies are usually yellow, smooth, and viscid (i.e., gummy) (García-Ochoa et al., 2000).

All members of the *Xanthomonas* genus are plant pathogens that infect a wide variety plants (García-Ochoa et al., 2000). Different *X. campestris* strains are the causative agents of many plant diseases, including black rot in members of the *Brassicaceae* family—such as cauliflower, broccoli and cabbage—and common bacterial blight of bean. *Xanthomonas* species (with the exception of *X. maltophilia*) are plant-associated bacteria that are not typically encountered in other environments (Hayward, 1993). *X. campestris* is not known to be pathogenic or toxic to humans (21 CFR 172.695).

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[1] A secondary metabolite is a molecule produced by a microorganism that is not essential to its growth but serves survival functions. Other examples of secondary metabolites of microorganisms include antibiotics and cholesterol-lowering drugs (Demain and Fang, 2000; Ruiz et al., 2010).

Xanthan gum is commercially produced by pure-culture fermentation of a carbohydrate with *X. campestris*. The gum is recovered from the fermentation broth using alcohol precipitation. It is then dewatered, dried, and milled into a fine powder (García-Ochoa et al., 2000). A complex growth medium is needed for the biofermentation of xanthan gum, including a carbohydrate source, nitrogen source, and several micronutrients (e.g., potassium, iron, and calcium salts) (García-Ochoa et al., 2000). Glucose and sucrose are the most commonly used carbohydrates in the production of food-grade xanthan gum (Palaniraj and Jayaraman, 2011; García-Ochoa et al., 2000). Glucose syrup used in the fermentation process is usually derived from maize (i.e., corn) or wheat (Biopolymer International, 2015).

The fermentation process most commonly used to produce xanthan gum takes about 100 hours in a stirred tank fermenter while oxygen is bubbled through the liquid (Palaniraj and Jayaraman, 2011). The pH must be maintained near 7.0 through the addition of a buffer or base such as potassium hydroxide (KOH) (García-Ochoa et al., 2000; Kuppuswami, 2014).

Before xanthan gum can be separated from the fermentation broth, the bacterial cells are deactivated, lysed (i.e., broken open), and/or removed. Usually, the broth is pasteurized to kill the bacterial cells, and the cells are removed from the diluted broth using centrifugation or filtration (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011). Xanthan gum is separated from the remaining mixture by precipitation with isopropyl alcohol in accordance with U.S. Food and Drug Administration (FDA) regulations (21 CFR 172.695). The gum is mechanically dewatered by means of pressing or centrifugation (Kuppuswami, 2014). After that, it may be washed with a salt solution (e.g., potassium chloride) to achieve the desired purity and dewatered again (Palaniraj and Jayaraman, 2011). Finally, the precipitate is dried and milled to a fine powder (García-Ochoa et al., 2000).

Properties of the Substance:

Commercial formulations of xanthan gum are dry, odorless, off-white to pale yellow, free-flowing powders or granules that are water soluble (Kuppuswami, 2014; García-Ochoa et al., 2000; Bergfeld et al., 2012). According to the manufacturer Cargill, xanthan gum is highly soluble in both hot and cold water, as its negatively charged side chains enhance its ability to dissolve (Cargill, 2016b). Xanthan gum is available in different mesh sizes and grades, such as rapidly hydrating, brine-tolerant, and/or clarified grade (i.e., larger particle size containing little to no dust to yield clear solutions) (Seisun, 2010). Xanthan gum's pH is near neutral by itself (Bergfeld et al., 2012), and xanthan gum is stable at a wide range of pH. The viscosity of xanthan gum solutions is stable at a wide range of temperatures and can withstand freeze-thaw cycles (Palaniraj and Jayaraman, 2011). According to the manufacturer Cargill, the viscosity of xanthan gum solutions is also unaffected by the addition of even large amounts of salt (Cargill, 2016b).

Xanthan gum solutions are highly pseudoplastic, meaning that they exhibit low viscosity when shear forces are applied, but they immediately regain their initial viscosity when shear forces are removed. This occurs because applied shear force disrupts the network of entangled, stiff xanthan molecules (Sworn, 2009). The pseudoplasticity of xanthan gum solutions is important during the processing of food products (e.g., for ease of filling, pouring, pumping, and spraying). It is also important for the desired cling and mouthfeel of food products (Sworn, 2011). Xanthan gum solutions are more pseudoplastic than most other food thickeners and they develop a higher viscosity at much lower concentrations (Sworn, 2011).

Specific Uses of the Substance:

Xanthan gum is used as a food additive in a wide variety of processed foods, including baked goods, beverages, dairy products, dressings, dietetic foods and beverages, dry mixes, frozen foods, gravies, meat products, pet foods, sauces, fruit preparations, soups, syrups, and toppings (Kuppuswami, 2014; Palaniraj and Jayaraman, 2011; Van Dyne, 2015). Xanthan gum can function as a thickener, stabilizer, emulsifier, suspending agent, bodying agent, and foam enhancer in foods (21 CFR 172.695). It is primarily added to improve flavor release, appearance, water-control properties, and viscosity of food. Some of the functions of xanthan gum in specific food products are provided in Table 1; however, this list is not complete due to the wide variety of applications of xanthan gum in many different processed foods.

Typical usage levels for xanthan gum in food range from 0.05% to 0.5% by weight (García-Ochoa et al., 2000; Sworn, 2009; Jungbunzlauer, 2015; TIC Gums, Inc., 2015a). According to one manufacturer (CP Kelco), xanthan gum is usually present at less than 0.05% in foods due to its self-limiting nature (Van Dyne, 2015). It is often added with other gums, such as guar gum or locust bean gum, to augment stabilization and binding (Palaniraj and Jayaraman, 2011). Xanthan gum is commercially available to consumers for use in gluten-free baking and other recipes (Rimmer, 2015).

Table 1: Uses of Xanthan Gum in Food Products

Food Application/Product	Function of Xanthan Gum	Sources
Salad dressings	Provides easy pourability, good cling; stabilizes emulsions; provides desirable body and improves flavor release; acts as partial replacement for starch or fat in reduced calorie dressings	Sharma et al., 2006; García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011; U.S. FDA, 2010
Bakery products	Binds water during baking and storage; extends shelf life; improves texture; acts as an egg replacer in soft baked goods; provides expected texture in reduced-fat foods	Sharma et al., 2006; U.S. FDA, 2010
Beverages	Enhances mouthfeel; suspends fruit pulp; stabilizes the suspension of insoluble ingredients	Palaniraj and Jayaraman, 2011; García-Ochoa et al., 2000
Dry mixes	Provides enhanced body and rapid viscosity development to reconstituted drinks; eases dispersion in hot or cold water	Palaniraj and Jayaraman, 2011; García-Ochoa et al., 2000
Frozen foods	Improves freeze/thaw stability; retards formation of ice or sugar crystals	García-Ochoa et al., 2000; Kuppuswami, 2014
Relishes	Maintains uniform distribution and eliminates loss of liquor during handling	Palaniraj and Jayaraman, 2011; Rosalam and England, 2006
Syrups and toppings	Increases viscosity and thickness/firmness; improves freeze-thaw stability	Palaniraj and Jayaraman, 2011; García-Ochoa et al., 2000
Pet foods	Stabilizes, binds ingredients in canned gravy based food; produces gelled product along with locust bean gum or guar gum	Palaniraj and Jayaraman, 2011
Prepared foods	Stabilizes emulsions and suspensions; avoids syneresis (i.e., separation of a liquid from a gel)	Sharma et al., 2006
Soups, sauces, and gravies	Provides temperature stability; prevents separation	Palaniraj and Jayaraman, 2011
Dairy products	Inhibits syneresis; stabilizes emulsions; improves consistency, body, and viscosity control; provides expected texture and creamy mouthfeel in reduced-fat foods	Sharma et al., 2006; García-Ochoa et al., 2000; U.S. FDA, 2010
Gluten-free breads	Mimics viscoelastic properties of gluten; provides desired crumb structure	Hager and Arendt, 2013
Meat products	Binds water; inhibits syneresis; provides viscosity for marinades	Palaniraj and Jayaraman, 2011; Lamkey, 2009

In addition to its uses in the food industry, xanthan gum is used in cosmetics (Bergfeld et al., 2012), personal care products (e.g., toothpaste, shampoo, lotions), pharmaceuticals, household cleaners, polishes, water-based paints, adhesives, and agricultural chemicals. It is also used in the textile, paper, oil drilling, and enhanced oil recovery industries (Palaniraj and Jayaraman, 2011).

Approved Legal Uses of the Substance:

Xanthan gum has been approved by FDA for use as a food additive without any specific quantity limitations. FDA requires that food-grade xanthan gum be derived from *X. campestris* by a pure-culture fermentation process and purified by recovery with isopropyl alcohol (residual isopropyl alcohol not to exceed 750 parts per million (ppm)). Also, food-grade xanthan gum must be manufactured as the sodium, potassium, or calcium salt (21 CFR 172.695). As stated in the Summary of Petitioned Use, xanthan gum is currently included on the National List as a nonagricultural (nonorganic), synthetic substance allowed as an ingredient in or on processed products labeled "organic" or "made with organic (specified ingredients or food group(s))" (7 CFR 205.605[b]).

Xanthan gum has also been approved by FDA for use in the preparation of cheeses and related cheese products under specific limitations. In cold-pack cheese food, xanthan gum levels may not exceed 0.3% of the weight of the finished food (21 CFR 133.124). In the particular case of Neufchatel cheese spread and pasteurized cheese spread, xanthan gum may be used alone or in combination with one or more substances on a particular list of ingredients, with the total quantity of such substances not to exceed 0.8%of the weight of the finished food (21 CFR 133.178, 133.179).

In addition, FDA has approved xanthan gum as an indirect food additive in paper, cardboard, and ethylene-vinyl acetate copolymers that may come into contact with food products. In paper and cardboard products, xanthan gum must adhere to the same standards as put forth in 21 CFR 172.695 (see above), but may only be used at a maximum level of 0.125% by weight of the finished paper. Furthermore, isopropyl alcohol residuals may not exceed 6,000 ppm in these products containing xanthan gum (21 CFR 176.170). Xanthan gum may also be used as a thickening agent at levels of less than 1% by weight of coating solids in aqueous dispersions of ethylene-vinyl acetate copolymers when these copolymers are used as coatings or as a part of coatings (21 CFR 177.1350).

FDA has also approved xanthan gum for use as a food additive permitted in feed and drinking water of animals (21 CFR 573.1010).

Xanthan gum is approved by U.S. Environmental Protection Agency (EPA) as a minimal risk inert ingredient in pesticide formulations and is exempt from the requirement of a tolerance on food items (40 CFR 180.950(e)).

Action of the Substance:

Xanthan gum is a hydrocolloid that adds many desired qualities to food items, typically in amounts ranging from 0.05% to 0.5% by weight (García-Ochoa et al., 2000; Sworn, 2009; Jungbunzlauer, 2015; TIC Gums, Inc., 2015a). Hydrocolloids are substances that disperse in water, providing a thickening or gelling effect. In the presence of salts or other hydrocolloids, these can produce gels or increase the viscosity of an item (Born et al., 2005). For example, when combined with locust bean gum, xanthan gum can form a gel; when combined with guar gum, xanthan gum solutions help increase viscosity. As a solid, xanthan gum molecules have a rigid helical structure. When melted in the presence of small quantities of salt, this rigid structure becomes disorganized but stable, which causes a thickening effect. High viscosities are achieved even when xanthan gum is present in small concentrations (Saha and Bhattacharya, 2010; Cargill, 2016b).

Xanthan gum and other hydrocolloids thicken solutions through the nonspecific entanglement of their long molecular chains (i.e., interactions not at specific binding sites). When hydrocolloids are present in a suspension in very dilute concentrations, their individual molecules can move freely and do not cause a thickening effect. As their concentration increases, movement of the molecules is restricted as they begin to come in contact with one another. The disordered molecular chains become entangled in a nonspecific way, and this transition to an entangled network is the process of thickening (Saha and Bhattacharya, 2010).

Xanthan gum is an effective suspending and dispersing agent, thickener, and stabilizer of emulsions, suspensions, and foams. It provides viscosity control, prevents separation of ingredients, increases water binding, and inhibits syneresis (the separation of liquid from a gel) (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011). Xanthan gum can stabilize food items at a wide range of pH and at high temperatures. It can also assist with flavor release and texturization (Palaniraj and Jayaraman, 2011).

Combinations of the Substance:

Xanthan gum may be used alone or in combination with other thickeners, stabilizers, emulsifiers, and gelling agents that are included on the National List and allowed for use in organic handling and processing. These include: carrageenan, guar gum, and locust bean gum (Palaniraj and Jayaraman, 2011); konjac flour (Cargill, 2016b); gum arabic (acacia gum) (Ingredients Network, 2016); alginates and pectin (Ward, 2007); and gellan gum and starches (Saha and Bhattacharya, 2010). Nonorganically produced guar gum, locust bean gum, and gum arabic may be used in processed products labeled as “organic” only when organic forms are not commercially available. A limited number of sources indicate that organic versions of these gums may be available (Danisco, undated; TIC Gums, Inc., 2015b).

Xanthan synergistically interacts with galactomannans[2], such a locust bean gum, guar gum, cassia gum, and tara gum, and with konjac glucomannan (Sworn, 2009). These interactions cause a synergistic increase in viscosity or gelation. While gelling is not one of xanthan gum’s major functions in food, it will help form a gel when combined with locust bean gum, konjac, or tara gum (Cargill, 2016b; Ingredient Solutions, Inc., 2016). Saha and Bhattacharya (2010) report that xanthan gum and guar gum (nongelling agents) are often combined with carrageenan and locust bean gum (gelling agents) to enhance viscosity of mixtures and elasticity of gels. They also report that xanthan gum can be combined with gellan gum to produce ready-to-eat dessert gels.

In baked goods, a combination of sodium alginates and xanthan gum may help increase batter viscosity and cake volume (Ward, 2007). In protein beverages, combining pectin with guar gum or xanthan gum can help stabilize the suspension (Ward, 2007).

Xanthan gum is often used in combination with starches to provide thickening and stability. While starches are the most commonly used hydrocolloid thickeners, other gums are often added to starches to improve the texture and mouthfeel of foods (Saha and Bhattacharya, 2010). In baked goods, xanthan gum helps to inhibit starch retrogradation (e.g., the staling of bread), thereby extending the shelf life of a product (Ward, 2007). In addition, xanthan gum may be added to starch gels to improve their freeze-thaw stability (Belitz et al., 2009).

Blends of xanthan gum, carrageenan, guar gum, and locust bean gum are used as stabilizers for frozen and chilled dairy products such as ice cream, sherbet, sour cream, whipping cream, and recombined milk (Sworn, 2009). These blends help to provide optimal viscosity, long-term stability, improved heat transfer during processing, protection from heat shock, and ice crystal control (Sworn, 2009). Xanthan gum is often added to carrageenan blends for use in meat brines and other meat applications (Lamkey, 2009). Commercially available blends also include xanthan gum and guar gum (Vedeqsa, 2010a), xanthan gum with both guar gum and locust bean gum (Vedeqsa, 2010b), and xanthan gum with gum arabic (acacia gum) (Ingredients Network, 2016).

Aside from the hydrocolloids mentioned above, additional ingredients or ancillary substances are not commonly added to commercially available forms of xanthan gum for use in foods (Wyard, 2015). Only a couple of exceptions to this were found through a search of publically available specification sheets. One commercially available xanthan and guar gum blend is standardized through the addition of glucose (Vedeqsa, 2010a). The product GRINDSTED® Xanthan Ultra is pre-dispersed by adding 1% polysorbate 60 (Danisco, 2006). Polysorbate 60 is a synthetic food additive not included on the National List.

Status

Historic Use:

Researchers at the Northern Regional Research Laboratory of the USDA discovered xanthan gum while identifying microorganisms that produced water-soluble gums of commercial interest. Industrial production of xanthan gum started in 1960, and substantial commercial production began in 1964 (Born et

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[2] Galactomannans are polysaccharides that are mostly extracted or isolated from plant seeds and consist mainly of the monosaccharides mannose and galactose (Wielinga, 2009).

al., 2005). By 1969, FDA gave approval for food use without any specific quantity limitations after toxicological and safety studies showed no significant health effects in short- and long-term feeding studies in rats or dogs and a reproduction study in rats (Kang and Pettitt, 1993). Approval in Canada occurred in 1971 (Pettitt, 1979); the FAO/WHO (Food and Agricultural Organization/World Health Organization) specifications were passed in 1974; and approval in Europe occurred in 1982 (Born et al., 2005). Many other countries have also approved xanthan gum for use in foods.

Worldwide annual production of xanthan gum is approximately 100,000 metric tons (Kreyenschulte et al., 2014), with about 65% being used by the food industry (Lopes et al., 2015). Global demand for xanthan gum is increasing as its range of applications is broadening (Lopes et al., 2015; Kuppuswami, 2014). Its versatility and unique properties have made it a hydrocolloid of choice in many industries (Kuppuswami, 2014).

Organic Foods Production Act, USDA Final Rule:

Xanthan gum is listed under 7 CFR 205.605(b) of the National List of Allowed and Prohibited Substances as a nonagricultural (nonorganic) substances allowed as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))." Xanthan gum is classified as a synthetic product, allowed with no further annotations.

International:

Canadian General Standards Board (CGSB)

Xanthan gum is permitted as a food additive for use in organic handling and processing in Canada according to the most recent November 2015 amendment of the Canadian Organic Production Systems Permitted Substances Lists. It may be derived using isopropyl alcohol or any other substances listed as extraction solvents, carriers, and precipitation aids in Table 6.3 of the standard (CGSB, 2015).

CODEX Alimentarius Commission

The Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme lists xanthan gum as a food additive permitted for use in organic food production to perform all functions in foods of plant origin. It is not permitted in foods of animal origin. Its use is restricted to fats and oils, fat emulsions, fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, nuts and seeds, bakery wares, and salads (e.g., macaroni salad, potato salad). Xanthan gum is considered an ingredient of nonagricultural origin that may be used in products labelled as organic (Codex Alimentarius Commission, 2013).

European Economic Community (EEC) Council Regulation, EC No. 834/2007 and 889/2008

The European Union allows the use of xanthan gum in the production of processed organic foods as a food additive in the preparation of foodstuffs of plant or animal origin with no specific limitations. It is classified as an ingredient of nonagricultural origin (Commission of the European Communities, 2008).

Japan Agricultural Standard (JAS) for Organic Production

Xanthan gum is allowed as a food additive under Article 4 of the Japanese Agriculture Standard for Organic Processed Foods. Article 4 addresses criteria of production methods for organic processed foods and allows xanthan gum as a food additive ingredient in processed foods of plants and animal origin. In the case of foods of animal origin, its use is limited to dairy or confectionary products (Japanese MAFF, 2012).

International Federation of Organic Agriculture Movement (IFOAM)

The International Federation of Organic Agriculture Movement (IFOAM) permits the use of xanthan gum as an additive in organic processed products with no further limitations or notes (IFOAM, 2014).

Other International Organic Standards

Xanthan gum is allowed for use in organic food processing as an additive only for fat, fruit and vegetable products, and cakes and biscuits by the Pacific Organic Standard (Secretariat of the Pacific Community, 2008) and by the East African Organic Product standard (East African Community, 2007).

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)).

Xanthan gum is commercially produced by aerobic fermentation using the bacterium *Xanthomonas campestris* in a broth containing a carbohydrate (usually glucose), a nitrogen source, and mineral salts. The gum is recovered from the fermentation broth using alcohol precipitation (Palaniraj and Jayaraman, 2011). The following factors can affect the yield and structure of the xanthan gum produced: type of fermentation vessel used, mode of operation (batch or continuous), medium composition, and culture conditions including temperature, pH, and dissolved oxygen concentration (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011).

Commercial production of xanthan gum involves several steps. The first step is selecting the appropriate strain of *X. campestris* to produce the desired properties and preserving it for long-term storage. Next, a small amount of the preserved culture is expanded using a multistage buildup from agar plates to shake flasks to small seed fermentation vessels to the final large fermentation vessel (Palaniraj and Jayaraman, 2011; Biopolymer International, 2015). The type of bioreactor used by most xanthan gum producers is the sparged stirred tank fermenter (sparging refers to bubbling oxygen through the liquid) (Palaniraj and Jayaraman, 2011).

A complex growth medium is utilized for the fermentation broth. *X. campestris* needs several micronutrients (e.g., potassium, iron, and calcium salts) and macronutrients (including carbohydrate and nitrogen sources) in order to produce xanthan gum (García-Ochoa et al., 2000).

Glucose and sucrose are the most commonly used carbohydrates in the production of food-grade xanthan gum (Palaniraj and Jayaraman, 2011; García-Ochoa et al., 2000). Biopolymer International, a world-wide association of xanthan gum manufacturers, reports that glucose syrup derived from maize (i.e., corn) or wheat is the main carbon source employed by its members (Biopolymer International, 2015). Other carbon substrates such as maltose, soluble starch, and agro-industrial waste products (e.g., sugar cane broth, sugar-beet molasses, and cheese whey) have been shown to be potential substrates for xanthan gum production (Kreyenschulte et al., 2014). Studies have indicated that the highest xanthan gum yield is achieved with 2–5% glucose as the carbon source (Kreyenschulte et al., 2014).

The source of nitrogen in the growth medium might be an organic compound, such as glutamate, and/or inorganic molecules, such as ammonium or nitrate salts (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011; Biopolymer International, 2015). The use of complex nitrogen sources such as yeast extract, soy-meal peptone, and soybean whey have also been reported (Palaniraj and Jayaraman, 2011).

Micronutrients added to the fermentation broth may include sources of potassium, phosphorus, sodium, magnesium, boron, zinc, iron, sulfur, calcium, and hydrogen (García-Ochoa et al., 2000). Small levels of organic acids such as succinic acid and citric acid may also be added to the growth medium to serve as pH buffering agents and nutrients for *X. campestris* (García-Ochoa et al., 2000; Carignatto et al., 2011).

During batch production of xanthan gum, the fermentation process is carried out for about 100 hours at a temperature of 25–34 degrees Celsius (Palaniraj and Jayaraman, 2011). The pH of the fermentation broth decreases due to the formation of acid groups present in xanthan gum. In order to maintain the pH of the broth at 7.0 (neutral), the pH is adjusted using a buffer or by adding of bases (e.g., KOH, NaOH, NH_4OH) (García-Ochoa et al., 2000). Potassium hydroxide (KOH) solution is the most common tool used to control the fermentation broth pH during production of xanthan gum (Kuppuswami, 2014).

Recovery of xanthan gum from the fermentation broth is difficult and costly due to the high viscosity of the broth. The main steps of recovery are deactivation and/or removal of the bacterial cells, precipitation of xanthan gum, dewatering, drying, and milling of the final product (Palaniraj and Jayaraman, 2011).

Many different methods are employed to deactivate, lyse, and remove the bacterial cells from the fermentation broth. The broth may be treated with chemicals (e.g., alkali, hypochlorite, enzymes), but care must be taken not to degrade the biopolymer (García-Ochoa et al., 2000). The types of enzymes employed for this are proteolytic and lytic enzymes that can break down the bacterial cells into low-molecular-weight molecules (Kuppuswami, 2014). Instead of using chemical treatment, the broth is usually pasteurized at 80–130 degrees Celsius to kill the bacterial cells (García-Ochoa et al., 2000). Following pasteurization, the broth may be diluted with water, alcohol, or mixtures of alcohol and salts in low quantities. This is done to reduce the viscosity. Then, the bacterial cell biomass is removed from the broth using centrifugation or filtration (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011).

Once the bacterial cells are removed from the broth, xanthan gum is separated from the remaining mixture using precipitation or concentration by evaporation (García-Ochoa et al., 2000). The most common technique applied is precipitation using water miscible nonsolvents for xanthan gum, such as isopropyl alcohol or ethanol (Kuppuswami, 2014). Current FDA food additive regulations require that food grade xanthan gum be purified by recovery with isopropyl alcohol (21 CFR 172.695). García-Ochoa et al. (2000) and Palaniraj and Jayaraman (2011) report that three volumes of isopropyl alcohol are needed per volume of broth to achieve total precipitation of the gum. The alcohol also functions to wash out impurities such as colored components, salts, and cells (García-Ochoa et al., 2000). Increasing the salt content of the fermentation broth prior to precipitation (usually done with potassium chloride) lowers the amount of isopropyl alcohol needed by about 30% (Kuppuswami, 2014). Likewise, when ultrafiltration is used to concentrate the fermentation broth prior to alcohol precipitation, the energy and alcohol requirements are greatly reduced (Lo et al. 1996; Lo et al., 1997).

Once xanthan gum is separated from the fermentation broth as a wet precipitate, it is mechanically dewatered by means of pressing or centrifugation (Kuppuswami, 2014). After that, it may be washed with a salt solution (e.g., potassium chloride) to achieve the desired purity and dewatered again (Palaniraj and Jayaraman, 2011). Finally, the precipitate is dried using forced-air driers (with an inert gas), vacuum driers, drum driers, or spray driers. The dried precipitate is milled to a powder with a predetermined mesh size and packed into containers with a low permeability to water (García-Ochoa et al., 2000; Palaniraj and Jayaraman, 2011; Kuppuswami, 2014).

Additional Information on Precursors and Feedstocks of Xanthan Gum

Regarding the use of genetically modified organisms (GMOs) during the production of xanthan gum, the manufacturer's association Biopolymer International released a position statement on its website which states that the microorganism used by its members to produce xanthan gum is not a genetically modified organism as defined in the EC (European Commission) Directives (Biopolymer International, 2005). No other sources were found to indicate the extent to which genetically modified strains of *X. campestris* are being used commercially. Biopolymer International also reports that some of the organic nutrients used by its members during fermentation may be derived from crops "for which genetically modified variants may be available besides the conventional ones." However, the nutrients are reportedly metabolized during fermentation, and their residues are removed during the extraction and purification steps (Biopolymer International, 2005). At least two commercial non-GMO xanthan products are available (TIC Gums, Inc., 2015a; Danisco, 2016). The manufacturers of these products report that the substrates and raw materials used during fermentation are not produced from GMOs.

<u>Evaluation Question #2:</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)). Discuss whether the petitioned substance is derived from an agricultural source.

The available sources indicate that xanthan gum for use as a food additive is created by a naturally occurring biological process, namely pure culture fermentation of a carbohydrate with the microorganism

X. campestris (see response to Evaluation Question #1). However, the commercially available sources of xanthan gum involve production steps that do not occur in nature. Xanthan gum is separated from the fermentation medium using precipitation with a synthetic, nonmiscible solvent (isopropyl alcohol). Physical and mechanical methods that are also used during the purification and processing of the final product may include: thermal pasteurization, filtration, ultrafiltration, centrifugation, washing with salt solutions (e.g., potassium chloride), and pressing. The following chemical methods may also be used by some manufacturers: deactivation of the bacterial cells in the broth using chemicals such as alkali, hypochlorite, or proteolytic and lytic enzymes that may unintentionally alter the xanthan gum (i.e., by removing pyruvate groups from the side chains) (García-Ochoa et al., 2000). However, these chemical methods are not necessary if pasteurization is used.

As described above, pure culture fermentation is the primary method of fermentation used to commercially produce xanthan gum. In this type of fermentation, a single species of microorganism is grown. Another type of fermentation process used in the food industry is mixed-culture fermentation, a process that involves multiple species of microorganisms. Mixed-culture fermentation is the norm in nature because many types of microorganisms exist together and compete for resources (Hesseltine, 1992).

The complex liquid growth medium that is utilized for the fermentation of xanthan gum is not an agricultural source; however, some of the possible substrates and nutrients used during fermentation are agricultural sources or derived from agricultural sources. These include glucose, sucrose and maltose syrups, soybean whey, soy-meal peptone, sugar cane broth, sugar-beet molasses and cheese whey.

During the fermentation of xanthan gum, conditions must be carefully controlled for optimal yield, structure, viscosity, and flow behavior (García-Ochoa et al., 2000; Lopes et al., 2015). These conditions include temperature, pH, agitation speed, aeration, and fermentation time (Lopes et al., 2015). The manufacturer CP Kelco reports that, "The composition and structure of xanthan gum produced by commercial fermentation is identical to the naturally occurring polysaccharide formed by *Xanthomonas campestris* on plants belonging to the cabbage family" (CP Kelco, 2016). No sources were found that directly contradict this assertion; however, the molecular weight of xanthan gum and the extent of pyruvic acid and acetyl substitutions on the side chains of the xanthan gum compound are known to depend upon variables such as the specific *Xanthomonas* strain used for fermentation, the composition of the fermentation medium, and the operational conditions used (García-Ochoa et al., 2000). Natural variations in the structure of xanthan gum are known to occur, and an increased understanding and control of its structural changes in the future could lead to new and improved uses of xanthan gum (Sworn, 2009).

As mentioned in response to Evaluation Question #1, chemicals (e.g., alkali, hypochlorite, enzymes) may be used to deactivate or kill the bacterial cells once fermentation of xanthan gum is complete (García-Ochoa et al., 2000). These chemicals may unintentionally alter the xanthan gum molecule causing removal of some of the pyruvate groups from the side chains. However, most of the available sources do not mention the use of chemical methods to deactivate or kill the bacterial cells. Instead, the fermentation broth is usually pasteurized to kill the bacterial cells (García-Ochoa et al., 2000). The manufacturer's association Biopolymer International (whose members include six major xanthan gum producers) reports that the fermentation broth is pasteurized to kill all the bacterial cells (Biopolymer International, 2015).

As stated in FDA regulations, food-grade xanthan gum is manufactured as a sodium, potassium, or calcium salt (21 CFR 172.695). The presence of glucuronic acid and pyruvate groups on the side branches, as shown in Figure 1, give xanthan gum a highly negative charge. Manufacturers neutralize these acid groups by adding positively-charged sodium, potassium, or calcium ions (Cargill, 2016b).

Current FDA food additive regulations require that food-grade xanthan gum be purified by recovery with isopropyl alcohol specifically (21 CFR 172.695). Written public comments from the manufacturer CP Kelco and the Organic Materials Review Institute (OMRI) report that during the alcohol precipitation step, xanthan gum is recovered from the fermentation broth without chemically altering the xanthan gum (Van Dyne, 2015; Miars and Fernandez-Salvador, 2015). Isopropyl alcohol is added to the fermentation broth to cause the xanthan gum compound to precipitate out of solution. Xanthan gum is highly soluble in hot and cold water. To separate it from the aqueous fermentation broth, the solvent isopropyl alcohol is added because xanthan gum in not miscible in this solvent. Adding this solvent reduces the solubility of xanthan gum until phase separation occurs and xanthan gum forms a solid precipitate (García-Ochoa et al., 2000). In addition, impurities in the fermentation broth, such as colored components, salts, and cells are "washed out" with the isopropyl alcohol (García-Ochoa et al., 2000). OMRI reports that residual isopropyl alcohol is removed from the xanthan gum using flash evaporation (Miars and Fernandez-Salvador, 2015), but no mention of this was found the in the other available sources. FDA regulations require that the final food additive contains no more than 750 ppm residual isopropyl alcohol (21 CFR 172.695). No other information was found to suggest any other synthetic materials used in the production and extraction of xanthan gum may remain in the final product. The Food Chemicals Codex (FCC) monograph for xanthan gum lists impurity acceptance criteria only for lead, isopropyl alcohol, and ethanol (which may be used for precipitation of xanthan gum products not sold in the U.S.) (U.S. Pharmacopeia, 2012).

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)).

Although xanthan gum is produced in nature by *Xanthomonas campestris* and related bacterial species, there is no evidence that other commercially available natural sources of xanthan gum exist. All commercial-scale xanthan gum manufacturing for use as a food additive begins with a naturally occurring biological process (i.e., pure-culture fermentation) that takes place in an artificially controlled production system (e.g., temperature and pH are regulated for optimal yield). Synthetic nutrients are used in the fermentation process, and the xanthan gum is recovered from the fermentation broth by precipitation with a synthetic solvent (isopropyl alcohol).

Based on the most commonly used manufacturing techniques reported in the available sources (both from manufacturers and scientific literature), no chemical modifications occur to the xanthan gum molecule after it is produced during fermentation. The only exception to this may be if chemicals such as alkali, hypochlorite, or proteolytic and lytic enzymes are used during the recovery and purification process that intentionally or unintentionally alter the xanthan gum molecule (e.g., depyruvylation of the side chains) (García-Ochoa et al., 2000); however, most of the available sources do not mention the use of these chemical methods.

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.

Xanthan gum it is not affirmed as GRAS by FDA (U.S. FDA, 2015a); however, three different xanthan gum preparations have been the subject of GRAS notices (U.S. FDA, 2015b). In a response letter to GRAS Notice No. 000121, FDA had no questions regarding Ingredients Solutions' conclusion that xanthan gum purified by recovery with ethyl alcohol (ethanol) is GRAS (Tarantino, 2003). Similarly, in a response letter to GRAS Notice No. 000211, the agency had no questions regarding Kelco's conclusion that xanthan gum (reduced pyruvate) is GRAS (Tarantino, 2007). Finally, in a response letter to GRAS Notice No. 000407, FDA had no questions regarding Inovo Biologic's conclusion that a polysaccharide complex of konjac glucomannan, sodium alginate, and xanthan gum is GRAS (Keefe, 2012).

Although FDA had no questions as to the GRAS status of xanthan gum purified by recovery with ethanol and reduced pyruvate xanthan gum under the intended conditions of use in foods, the agency did note that those particular xanthan gum preparations do not comply with current FDA food additive regulations for xanthan gum (21 CFR 172.695), which require the use of isopropyl alcohol for the recovery step and pyruvic acid content greater than 1.5% by weight. Therefore, the xanthan gum food additive regulation would have to be amended before those preparations could be legally used in foods.

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)).

The primary technical functions of xanthan gum in foods include stabilizer, emulsifier, thickener, suspending agent, bodying agent, and foam enhancer (21 CFR 172.695). As a result of those functions, xanthan gum may also help to extend the shelf life of some products. Therefore, preservative could be considered one of xanthan gum's secondary technical functions in foods.

As shown in Table 1, xanthan gum is used in many different food categories to stabilize emulsions, prevent formation of ice crystals in frozen foods, inhibit syneresis (the separation of a liquid from a gel), or bind water during the storage of a food item. These all help to preserve desirable characteristics in processed food items. The trade association International Food Additives Council (IFAC) reports that xanthan gum is used in bakery fillings to prevent water migration from the filling to the pastry, and that xanthan gum can often be used to extend the shelf life of a product (IFAC, 2015). In addition, xanthan gum helps to inhibit starch retrogradation (e.g., the staling of bread), thereby extending the shelf life of baked goods (Ward, 2007).

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)).

Although xanthan gum functions to enhance the flavor and texture of many foods, there is no indication that it is used to restore those characteristics after being lost due to processing. No information was found to suggest that xanthan gum is used to recreate or improve flavors, colors, textures, or nutritive values lost during processing.

Many of today's processed foods are manufactured to exhibit specific texture, viscosity, and flavor release specifications that xanthan gum provides (Lopes et al., 2015; Palaniraj and Jayaraman, 2011). Xanthan gum is used to produce the desired texture in ice cream and other frozen foods (Cargill, 2016c), enhance the body and texture of beverages, and improve the texture of baked goods (Palaniraj and Jayaraman, 2011). It is also used to improve flavor release in salad dressings, sauces, gravies, dairy products, and bakery fillings (Palaniraj and Jayaraman, 2011).

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)).

No information was found to indicate that xanthan gum has a negative or positive effect on the nutritional quality of the food to which it is added; however, xanthan gum is a soluble dietary fiber, and has the potential, along with other dietary fibers, to decrease mineral availability in the intestines (Baye et al., 2015). This potential is based on laboratory studies that have shown how various fibers have mineral-binding properties *in vitro* (e.g., cellulose, caboxymethylcellulose, lignin, pectin, psyllium, alginic acid, guar gum, locust bean gum, xanthan gum, agar, carrageenan, gum arabic, gum karaya, gum tragacanth). By contrast, animal and human *in vivo* studies of various soluble dietary fibers have failed to demonstrate negative effects on mineral absorption, and some *in vivo* studies with fibers (e.g., pectin, fructooligosacccharides) have shown positive effects on mineral absorption (Baye et al., 2015). One possible reason for the difference observed between laboratory and *in vivo* studies is that fermentation of the fibers in the colon may free bound minerals and offset the negative mineral-binding effects of the fibers (Baye et al., 2015). The effect of dietary fibers on mineral absorption in humans is still unclear (Baye et al., 2015).

In one laboratory study, the addition of xanthan gum to standard infant formula showed no effect on the availabilities of calcium, iron, or zinc; however, the availabilities of other nutrients were not studied (Bosscher et al., 2003). In another laboratory study, xanthan gum was shown to bind zinc, calcium, and iron in solutions (Debon and Tester, 2001). No other laboratory or human studies were found that assessed the effects of xanthan gum on the absorption of minerals and trace elements.

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

No reports of residues of heavy metals or other contaminants in excess of FDA tolerances have been identified for xanthan gum. The requirements for xanthan gum in the 8th edition of the "Food Chemicals Codex" specify that it contain no more than 2 mg/kg lead (U.S. Pharmacopeia, 2012). No substances listed on FDA's Action Levels for Poisonous or Deleterious Substances in Human Food have been reported as contaminants of concern in xanthan gum.

<u>Evaluation Question #9:</u> 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)).

No sources were identified that discussed environmental contamination resulting from the commercial manufacturing of xanthan gum. The organic solvent used to separate xanthan gum from the fermentation broth (isopropyl alcohol) is recovered by distillation and reused (Kuppuswami, 2014; Lopes et al., 2015).

Xanthan gum is a naturally occurring, biodegradable polysaccharide (Muchová et al., 2009) that is considered by EPA to be a minimal risk inert ingredient in pesticide formulations (40 CFR 180.950(e)). No sources were identified that discussed whether the use of xanthan gum as a food additive may be harmful to the environment or biodiversity.

Xanthan gum is degraded only by certain microorganisms with xanthanase enzyme activity, and the degradation products of xanthan gum are naturally occurring monosaccharides (i.e., single sugars) that make up its structure (Ruijssenaars et al., 1999). In a laboratory study, xanthan gum was readily degraded by microorganisms from human feces or soil (Ruijssenaars et al., 2000).

Because bacteria in the human gut have limited capacity to degrade xanthan gum during its transit time through the intestines, it has the potential to enter wastewater (Muchová et al., 2009). One study tested the biodegradability of xanthan gum in activated sludge obtained from a wastewater treatment plant. This study found that xanthan-degrading bacteria were present in the activated sludge, and xanthan gum was readily degraded with complete biodegradation occurring in about 10 days (Muchová et al., 2009).

<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)).

Xanthan gum is an FDA-approved direct food additive that that has been used since 1969 with no specific quantity limitations. In 1986, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an Acceptable Daily Intake (ADI) for xanthan gum as "not specified," meaning that the total dietary intake of xanthan gum when used as a food additive does not represent appreciable risk to human health (JECFA, 1986). Xanthan gum is a soluble dietary fiber (Chawla and Patil, 2010); following ingestion, xanthan gum passes through the intestinal tract largely unabsorbed (JECFA, 1986).

Toxicological studies conducted at its discovery in the early 1960s showed no long- or short-term effects in dogs or rats, and no reproductive effects in rats (Woodward et al., 1973). Subsequent short-term animal studies were conducted on guinea pigs and rabbits in the following two decades. No consistent toxicity or carcinogenicity was observed (JECFA, 1986). Toxicity investigations in overweight humans began as early as 1974 and continued through the mid-1980s. In these studies, no adverse effects were documented at daily levels of up to 10–13 g xanthan gum for 23 days (JECFA, 1986; Eastwood et al., 1987).

While xanthan gum is recognized as safe by FDA when used in accordance with 21 CFR 172.695, it is not affirmed as GRAS by FDA (U.S. FDA, 2015a). As detailed in response to Evaluation Question #4, FDA had no questions as to the GRAS status of xanthan gum in three separate GRAS notices for various xanthan gum preparations intended for use in foods (U.S. FDA, 2015b). These include xanthan gum purified by recovery with ethanol (Tarantino, 2003), a reduced pyruvate form of xanthan gum (Tarantino, 2007), and xanthan gum used in combination with konjac glucomannan and sodium alginate (Keefe, 2012). While FDA had no questions as to the GRAS status of these forms of xanthan gum, the first two preparations do not comply with current FDA food additive regulations for that require xanthan gum to be purified by recovery with isopropyl alcohol and to contain greater than 1.5% pyruvic acid by weight (21 CFR 172.695).

Dietary supplementation with xanthan gum has been studied for its potential health benefits in humans. A 1985 study in healthy and diabetic subjects showed that feeding xanthan gum (12 g/day) for six weeks in muffins significantly lowered blood sugar levels as well as plasma cholesterol levels in diabetic subjects only (Osilesi et al., 1985). Daly et al. (1993) studied xanthan gum's effectiveness as a bulk laxative in healthy adult males. This study demonstrated that ingestion of 15 g/day of xanthan gum for ten days increased stool bulk, frequency of stools, and flatulence. This study also showed that fecal bacteria from the subjects at the end of the exposure period showed an increase in the production of short chain fatty acids (SCFA), which are believed to be beneficial to colon health (Ríos-Covían et al., 2016).

In 2011, the European Food Safety Authority (EFSA) reviewed the available scientific studies related to the claim that xanthan gum, when used as a dietary supplement, causes desired changes in bowel function such as reduced transit time, more frequent bowel movements, increased fecal bulk, and softer stools. The EFSA concluded that there was no established cause and effect between xanthan gum consumption and changes in bowel function due to lack of scientific evidence from properly controlled studies (EFSA, 2011). Despite its long history of safe use in foods, some adverse effects relating to xanthan gum have been reported in the sources described below.

In 2011, FDA announced a press release and consumer advisory warning parents, caregivers, and health care providers not to feed SimplyThick® to premature infants because of a possible link between the product and the disease necrotizing enterocolitis (NEC) (U.S. FDA, 2011a). NEC is a gastrointestinal disease process that occurs mostly in premature neonates characterized by inflammation and bacterial invasion of the bowel wall (Thompson and Bizzarro, 2008). It is the most common life-threatening gastrointestinal emergency experienced by premature infants in neonatal intensive care units (Gregory et al., 2011), occurring in about 5-10% of very low birthweight infants (<1500 g) (Thompson and Bizzarro, 2008). The cause of NEC has not definitively been identified although it is believed to be caused by multiple factors. Three factors that are areas of research include intestinal injury (e.g., ischemia/oxygen deprivation to the tissue) and inflammation, issues relating to enteric (i.e., tube) feeding, and alterations in the normal bacterial colonization of the GI tract (Gregory et al., 2011). SimplyThick® is a xanthan-gum based food and beverage thickener that is designed to help people who have swallowing difficulties. Prior to the FDA press release warning that it may be linked to NEC, it was being recommended by health care providers to thicken breast milk and infant formula for premature infants with swallowing difficulties or gastroesophageal reflux both in the hospital and once discharged home (Beal et al., 2012). Less than a month after FDA's press release, SimplyThick® voluntarily recalled its thickening gel product manufactured at its Stone Mountain, Georgia, plant. SimplyThick®'s recall was reported to be associated with the occurrence of harmful bacteria of possible public health significance not being properly destroyed during manufacturing (U.S. FDA, 2011b). Manufacturing of the product continued at other locations.

In September 2012, FDA released a consumer update on the SimplyThick® investigation (U.S. FDA, 2012). Since the time of the May 2011 FDA press release, twenty-two infants were identified as developing NEC after being fed SimplyThick®, fourteen needed surgery, and seven died. The xanthan gum mixture was fed to infants for varying amounts of time. FDA warned caregivers that infants of any age should not be fed SimplyThick®. During FDA's investigation, it was discovered that one of the 22 babies affected was not a premature baby (U.S. FDA, 2012). In addition, many cases of premature infants being fed SimplyThick® were found to exhibit late-onset NEC, rather than typical NEC (Woods et al, 2012; Beal et al, 2012). A potential mechanism by which SimplyThick® may have predisposed the infants to NEC is through the accumulation of SCFAs produced by bacteria in the intestines breaking down the xanthan gum component of the mixture (Beal et al., 2012). In the 2012 consumer update, FDA reported that further study is needed to determine if there is an actual link between SimplyThick® and the development of NEC; however, FDA warned everyone involved in the care of infants of any age to be aware of the potential risks SimplyThick®. No further public communications have come from FDA on this issue and no studies were identified that establish a causal relationship between xanthan gum and NEC.

A 1990 occupational exposure study examined the relationship between workers exhibiting flu-like symptoms and their handling of xanthan gum powder in a plant that used a fermentation process to manufacture xanthan gum. Nose and throat irritation were more commonly reported by workers who experienced the greatest exposure to xanthan gum powder; however, no significant changes were found when workers were examined for acute changes in pulmonary function. No evidence of chronic pulmonary function problems were observed in any employees, regardless of exposure quantity or duration (Sargent et al., 1990).

A recent laboratory study demonstrated that xanthan gum has the potential to elicit an immune response in certain individuals (Vojdani and Vojdani, 2015). In this study, blood sera from healthy adults of the general population were screened for immunoglobulin G (IgG) and immunoglobulin E (IgE) antibodies against several different food additive gums including xanthan gum using ELISA testing (enzyme-linked immunosorbent assay). Results showed that 10% of the samples showed elevated IgG antibodies against xanthan gum and 16% showed elevated IgE antibodies against xanthan gum. Results for xanthan gum were comparable to the other gums tested which included mastic gum, carrageenan, guar gum, gum tragacanth, locust bean gum, and β-glucan. The authors concluded that some people may be suffering from hidden allergies to food gums (Vojdani and Vojdani, 2015). No other peer-reviewed sources were found that document allergic responses or specific symptoms in consumers with xanthan gum when used as a food additive.

As mentioned in response to Evaluation Question #1, some of the ingredients used as nutrients in the fermentation of xanthan gum are derived from food allergens (e.g., wheat, soy, dairy). According to the manufacturer DuPont/Danisco, those substrates are consumed during fermentation, and their own ELISA testing has confirmed no allergenic protein is detectable in GRINDSTED® Xanthan products to a quantification limit of 10 parts per million (ppm) for soy and 5 ppm for wheat (Danisco, 2009). According to another manufacturer, Archer Daniels Midland Company, their xanthan gum products (NovaXan™) do not contain detectable levels of major allergens, including wheat, gluten, dairy, or soy [ADM, undated(a)]. No other xanthan gum manufacturers provide food allergen information for their products in publically available sources. There is no documentation in the scientific literature that consumers with food allergies to wheat, soy, or dairy may have reactions to xanthan gum.

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

No studies were identified that compared the specific use of xanthan gum as a food additive with alternative practices. Food processors have the option of replacing xanthan gum with an agricultural ingredient that can function as a thickener, stabilizer, or emulsifier (see responses to Evaluation Questions #12 and 13) or creating products without the use of hydrocolloids; however, this may substantially alter the viscosity, processing capabilities, shelf life, sensory properties, and consumer acceptance of the food products.

<u>Evaluation Question #12:</u> 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)).

There are many natural hydrocolloids (i.e., substances that disperse in water, giving a thickening or gelling effect) that are possible alternatives for xanthan gum in food applications. These include both agricultural and nonagricultural substances. Traditionally, the agricultural substances starch and gelatin were ingredients used to provide the desired textural properties in foods; however, the modern large-scale processing industry places many demands on the thickeners and gelling agents that are utilized (Imeson, 1997). Natural additives that have been used successfully as thickeners, stabilizers, and/or emulsifiers in various processed food products include unmodified (native) starches; galactomannans such as guar gum, locust bean gum, and tara gum (only allowed if organic); gum arabic (acacia gum); gum karaya (only allowed if organic); gum tragacanth; pectin; and konjac flour (Saha and Bhattacharya, 2010; Seisun, 2010). According to the manufacturer Archer Daniels Midland Company (ADM), the natural substance lecithin (not a hydrocolloid) is widely used as an emulsifier, aerating agent, viscosity modifier, and dispersant in baked goods, confectionaries, dairy products (including ice cream as a stabilizer), instant beverage mixtures, sauces, and gravies [ADM, undated(b)]. Natural gelling agents that have been used in processed food products include the agricultural substances gelatin and pectin, and the nonagricultural substances agar-agar, carrageenan, and gellan gum (Saha and Bhattacharya, 2010). In addition, a wide variety of new plant-based gums are being investigated for use as thickeners, stabilizers, emulsifiers, texture modifiers, syneresis inhibitors, and gelling agents to meet the high demand in the food industry (Timilsena et al., 2016).

While there are many natural hydrocolloids available, they may not be suitable for replacement of xanthan gum in a specific food application. Each one has specific strengths, weaknesses, and compatibilities that manufacturers consider when formulating ingredient recipes (Ward, 2007). Xanthan gum has been reported to exhibit unique rheological characteristics and better stability than most other hydrocolloids against high temperatures, high levels of salts, and extreme pH values (Kreyenschulte et al., 2014). For example, galactomannans such as guar gum and locust bean gum can degrade and lose viscosity at extreme pH and high temperatures (Williams and Phillips, 2009). Solutions of xanthan gum are more pseudoplastic than most other thickeners and develop higher viscosity at much lower concentrations (see Properties of Substance section) (Sworn, 2011). In addition, xanthan gum has the unique ability to interact synergistically or form gels with galactomannans such as guar gum, cassia gum, tara gum, and locust bean gum (Sworn, 2011). Written public comments from the Organic Trade Association reported that many organic handlers indicated in anonymous electronic surveys that there are no suitable natural or organic alternatives to xanthan gum for many specific food applications (Wyard, 2015).

Several hydrocolloids have been used in gluten-free bread formulations to improve structure, texture, consumer acceptance, and shelf life. Xanthan gum and the synthetic substance hydroxypropyl methyl cellulose are the most commonly used hydrocolloids in gluten-free breads; however, other natural hydrocolloids that have been used include pectin, gum arabic, locust bean gum, guar gum, psyllium, agar-agar, and carrageenan (Capriles and Arêas, 2014; Zannini et al., 2012).

The National List includes the following ingredients that may provide similar functionality to xanthan gum alone or when used in combinations:

§205.605(a) (Nonagricultural, nonsynthetics allowed)

- Agar-agar
- Carrageenan
- Gellan gum

§205.606 (Nonorganically-produced agricultural products allowed only when organic forms are not commercially available)

- Gelatin
- Gums—water extracted only (arabic; guar; locust bean; and carob bean)
- Konjac flour
- Lecithin (de-oiled)
- Pectin (nonamidated forms only)
- Native corn starch
- Tragacanth gum

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

Some of the natural hydrocolloids mentioned in response to Evaluation Question #12 are available in organic forms and may be used as alternatives to xanthan gum in certain food applications. If alternatives to xanthan gum are used in food products, substantial changes may occur in viscosity, processing capabilities, shelf life, sensory properties, and consumer acceptance of the food products.

Organic starches (e.g., corn, tapioca, potato, wheat, arrowroot, and rice) are possible alternatives for xanthan gum in some food applications. Starch is the most commonly used hydrocolloid thickener, and it does not impart a foreign taste like some gums (Saha and Bhattacharya, 2010). Organic starches are commercially available from many suppliers. Organic psyllium seed husk powder is commercially available (BI Nutraceuticals, 2016). Organic locust bean gum, organic gum arabic, organic guar gum, and organic tara gum are also commercially available (Danisco, undated; TIC Gums, Inc., 2015b; Silvateam, 2016).

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