Tocopherols

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Tocopherols
5,7,8-Trimethyltocol (alpha-tocopherol)
5,8-Dimethyltocol (beta-tocopherol)
7,8-Dimethyltocol (gamma-tocopherol)
8-Methyltocol (delta-tocopherol)

Other Names:
Mixed tocopherols
Vitamin E

Trade Names:
CarolE™ ET and PT
Covi-ox®
Decanox™
Fortium® mixed tocopherols
Guardian® tocopherol extract
Nutrabiol® T
Sunvitol™ MT
Tocobiol®
Tocoblend®
Tocomix™
Vitapherole® T

CAS Numbers:
1406-66-2 (tocopherols)
59-02-9 (vitamin E/alpha-tocopherol)
148-03-8 (beta-tocopherol)
54-28-4 (gamma-tocopherol)
119-13-1 (delta-tocopherol)

Summary of Petitioned Use

Synthetic tocopherols have been included on the National List of Allowed and Prohibited Substances (hereafter referred to as the National List) since 2001. Synthetic tocopherols are currently permitted for use in organic agriculture handling/processing as an antioxidant ingredient in foods. Specifically, tocopherols derived from vegetable oil are allowed for use as ingredients in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group[s])" when rosemary extracts are not a suitable alternative (7 CFR 205.605[b]).

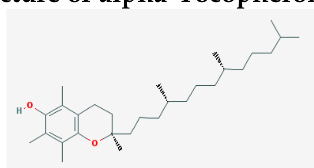
Characterization of Petitioned Substance

<u>**Composition of the Substance:**</u>
Tocopherols are a group of lipophilic phenolic antioxidants that occur naturally in a variety of plant species. Rich sources of naturally-occurring tocopherols include cereal grains, oilseeds, nuts, and vegetables (Burdock, 1997). The term "tocopherols" refers to structurally similar compounds that occur in nature in four forms: alpha-, beta-, gamma-, and delta-tocopherol (CIR, 2002). Tocopherols that are derived from plant products are often referred to as "mixed tocopherols" because the mixture contains all four forms of tocopherol (CIR, 2002). The molecular structure of each form of tocopherol consists of a chromanol ring connected to a long carbon side chain. Their structures vary in the number and position of the methyl groups on the ring (IOM, 2000; Burdock, 1997). The molecular structures and chemical formulas of the tocopherol compounds are shown in Figures 1–4.

The proportion of each of the tocopherol compounds present in a mixed tocopherols product is a reflection of the tocopherol profile of the particular vegetable oil(s) used to isolate the tocopherols (EFSA, 2008). A typical mixed tocopherols product consists primarily of gamma-tocopherol, followed by delta- or alpha-tocopherol, with beta-tocopherol usually the lowest proportion in the mixture (CIR, 2002; EFSA, 2008; Organic Technologies, 2013).

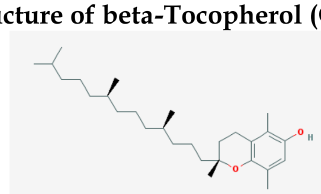
Mixed tocopherols for use as antioxidants in human foods are formulated as liquids or powders. Liquid mixed tocopherols are available on the market diluted with vegetable oil or prepared as synergistic mixtures with rosemary extracts, ascorbyl palmitate/ascorbic acid, or other antioxidants and synergists such as lecithin and citric acid (Pokorny et al., 2001; Kalsec, 2014a). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) specification for the food additive "mixed tocopherols concentrate" states that it may contain an edible vegetable oil added to adjust the required amount of total tocopherols (JECFA, 2006). Powdered mixed tocopherols contain a carrier such as tapioca starch, gum acacia, rice maltodextrin, calcium carbonate, or silica (Organic Technologies, 2013; BASF, 2013; Kemin, 2014b; NOSB, 1995; BTSA, 2013; BTSA, 2012). Table 1 identifies the manufacturer, brand name, formulation type, and ancillary substance(s) contained in various tocopherols products that are used as antioxidants in human foods.

Figure 1. Molecular Structure of alpha-Tocopherol (CAS# 59-02-9; $C_{29}H_{50}O_2$)



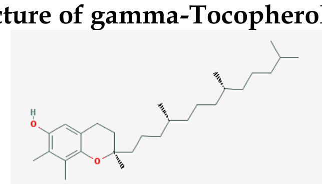
Source: PubChem Compound, 2014

Figure 2. Molecular Structure of beta-Tocopherol (CAS# 148-03-8; $C_{28}H_{48}O_2$)



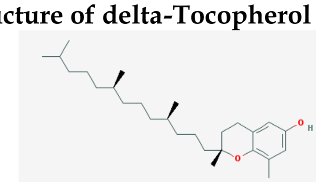
Source: PubChem Compound, 2014

Figure 3. Molecular Structure of gamma-Tocopherol (CAS# 54-28-4; $C_{28}H_{48}O_2$)



Source: PubChem Compound, 2014

Figure 4. Molecular Structure of delta-Tocopherol (CAS# 119-13-1; $C_{27}H_{46}O_2$)



Source: PubChem Compound, 2014

Table 1. Commercially Available Tocopherols Products Used as Antioxidants in Foods

Manufacturer	Product Name	Formulation	Ancillary Substance(s)	Source(s)
Advanced Organic Technologies (Buenos Aires, Argentina)	Tocomix™	Liquid	Sunflower oil	AOM, 2014
Archer Daniels Midland Company (Decatur, IL)	Decanox™	Liquid	Unknown	ADM, 2014
		Powder	Unknown	

Manufacturer	Product Name	Formulation	Ancillary Substance(s)	Source(s)
BASF (Germany)	Covi-ox®	Liquid	Soybean oil	Brenntag Specialties, Inc., date unknown; BASF, 2013
		Powder	Gum acacia	
BTSA (Madrid, Spain)	Tocobiol®	Liquid	Sterols, squalene, monodiglycerides*, soybean or sunflower oil	BTSA, 2014a; BTSA, 2013
		Powder	Calcium carbonate	
	Nutrabiol® T	Liquid	Soybean or sunflower oil	BTSA, 2014b; BTSA, 2012
		Powder	Silica	
DuPont Danisco (global)	Guardian® tocopherol extract	Unknown	Unknown	DuPont Nutrition and Health, 2014a
Kemin Industries, Inc. (Des Moines, IA)	Fortium® mixed tocopherols	Liquid	Sunflower oil	Kemin, 2014a; 2014b
		Powder	Rice maltodextrin	
Nutralliance (supplier) (Yorba Linda, CA)	Sunvitol™ MT	Powder	Unknown	Nutralliance, 2014
Organic Technologies (Coshocton, OH)	Natural mixed tocopherols	Liquid	Organic sunflower oil	Organic Technologies, 2013
		Powder	Tapioca starch	
Sigma-Aldrich (St. Louis, MO)	Mixed tocopherols	Liquid	Unknown	Sigma-Aldrich Co. LLC, 2014
The Scoular Company (Minneapolis, MN)	Natural source mixed tocopherols	Liquid	Unknown	The Scoular Company, 2014
		Powder	Unknown	
Vitablend (Wolvega, The Netherlands)	Tocoblend®	Liquid	Unknown	Vitablend, 2014
		Powder	Unknown	
VitaeNaturals (Toledo, Spain)	Vitapherole® T	Liquid	Unknown	Vitae Caps S.A., 2012
		Powder	Unknown	
Wilmar Spring Fruit Nutrition Products Co. (Jiangsu, China)	Natural mixed tocopherols	Liquid	Soybean or sunflower oil	Wilmar International Ltd., 2014
		Powder	Unknown	
ZMC-USA (The Woodlands, TX)	CarolE™ ET and PT	Liquid	Unknown	ZMC-USA, date unknown
		Powder	Unknown	

* Piñol del Olmo (date unknown) reports that sterols, squalene, and monodiglycerides are naturally present in Tocobiol® from the source vegetable oil.

Source or Origin of the Substance:

Tocopherols for use as antioxidants in foods are commonly extracted from the distillate obtained in the deodorization of vegetable oils (e.g., soybean, canola, sunflower, corn, cottonseed) (Burdock, 1997).

Tocopherols are separated from the other compounds in the oil distillate by multiple extraction and refining steps. These steps can include solvent extraction, chemical treatment, crystallization, complexation, and vacuum or molecular distillation (Burdock, 1997; EFSA, 2008; Torres et al., 2011). The total tocopherol content of the resulting product is usually 30–80% (Burdock, 1997); the remaining product consists of triacylglycerols (the main constituents of vegetable oil) (Pokorny et al., 2001). Liquid forms of mixed tocopherols are commercially available diluted in vegetable oils (Pokorny et al., 2001) and are also available as synergistic mixtures with rosemary extracts, ascorbyl palmitate/ascorbic acid, lecithin and/or citric acid (Pokorny et al., 2001; Kalsec, 2014a). Powdered forms of tocopherols are produced by spray-drying the liquid tocopherol oils onto a carrier or mixture of carriers (NOSB, 1995; ADM, 2014; Brenntag Specialties, Inc., date unknown).

Pokorny (2007) reported that natural tocopherol concentrate may also be obtained from wheat or corn germ. No other information was found on the use of wheat or corn germ as commercial sources of tocopherols.

Properties of the Substance:

The liquid form of tocopherols is described as a light brown to red viscous liquid with the odor of vegetable oil (JECFA, 2006). It is insoluble in water but miscible with oils and fats. The powdered form of tocopherols is described as a tan or tan-to-reddish colored powder that is water dispersible (Organic Technologies, 2013; ADM, 2014; Brenntag Specialties, Inc., date unknown).

Specific Uses of the Substance:

Tocopherols function as an antioxidant ingredient used for the stabilization of food products that contain lipids (i.e., fats and oil) susceptible to oxidative rancidity. Tocopherols protect food against oxidation reactions caused by free radicals (Shahidi and Wanasundara, 2011) (see the Action of the Substance section for more detail). This action helps to preserve the taste and nutritional value of the food. Tocopherols are used as additives in many different food categories including dairy products, cereals, frozen green vegetables, margarine, fresh and frozen sausages, vegetable oils, soft drinks, snacks and nuts, salad dressings, soup bases, seasonings, dehydrated potatoes, processed meats and poultry, and baked products (Shahidi and Wanasundara, 2011).

Typical usage levels of tocopherols in foods vary from about 100–450 parts per million (ppm) based on the fat or oil content of the food (Lampi et al., 2002; Brenntag Specialties, Inc., date unknown). Concentrations of up to 2,000 ppm may be necessary for oils containing highly polyunsaturated fatty acids (Brenntag Specialties, Inc., date unknown).

Tocopherols are used in dietary supplements and in a wide variety of cosmetic formulations, functioning as an antioxidant to protect the formulation and/or a skin conditioning agent. The usage levels are reported to be ≤5% in such products (CIR, 2002). Tocopherols are also used as an antioxidant ingredient in conventional livestock feed and pet food (ADM, 2014; Organic Technologies, 2013).

Approved Legal Uses of the Substance:

Tocopherols are permitted by the U.S. Food and Drug Administration (FDA) as chemical preservatives in every human food category and are affirmed as generally recognized as safe (GRAS) by FDA when used as chemical preservatives (21 CFR 182.3890) or nutrients (21 CFR 182.8890) in food for human consumption in accordance with good manufacturing practice. Their use is limited to 0.03% in rendered animal fats; however, a 30% concentration of tocopherols in vegetable oils shall be used when added as an antioxidant to products designated as ''lard'' or ''rendered pork fat.'' For meat products, levels are not to exceed 0.03% based on the total fat content and are not to be used in combination with other antioxidants. Levels of 0.03% or 0.02% (when in combination with other antioxidants) based on fat content are used in poultry products (9 CFR 424.21).

Tocopherols are also affirmed as GRAS by FDA when used as chemical preservatives (21 CFR 582.3890) and nutrients and/or dietary supplements in animal feeds (21 CFR 582.5890) in accordance with good manufacturing or feeding practice.

Action of the Substance:

Tocopherols are added to foods to help prevent oxidation of the fatty acids present in the lipid components of the food. Polyunsaturated fatty acids[1] are the least stable components of lipids and readily react with oxygen in the air (Pokorny, 2007). Saturated fatty acids[2] are oxidized as well, but at higher temperatures. Oxidation begins when oxygen is converted to highly reactive free radicals (e.g., oxygen ions, peroxides) by metal catalysis or exposure to light (Hardy and Roley, 2000). The free radicals attack fatty acids through the addition of oxygen atoms along their carbon chains. Upon oxidation, the fatty acids form more free radicals that start a chain reaction of further oxidation, eventually leading to the formation of secondary oxidation products—low molecular weight compounds including aldehydes, ketones, alcohols, and hydrocarbons. These compounds reduce the sensory qualities of the food by causing off-odors and off-flavors and changes in color and texture that together are referred to as oxidative rancidity of the food (Pokorny, 2007; Rasor and Duncan, 2014). Repeatedly consuming foods with oxidized lipids may be harmful to human health (Kanner, 2007). The addition of tocopherols at the optimum concentration in food can prevent oxidative rancidity (Pokorny, 2007).

Antioxidants are compounds that delay autoxidation by inhibiting the formation of free radicals or by interrupting the propagation of free radicals (Brewer, 2011). There are several different mechanisms by which antioxidants can delay autoxidation. Tocopherols are sacrificial antioxidants because they donate their phenolic hydrogen atoms to free radicals thereby converting them to stable and nonreactive forms. This prevents free radicals from attacking the fatty acids in the food (Hardy and Roley, 2000). In fats and oils, the antioxidant activity of the various tocopherols decreases in the order of delta > gamma > beta > alpha (Pokorny, 2007).

Combinations of the Substance:

Tocopherols can be used alone or in combination with other antioxidants and synergists such as rosemary extract, ascorbyl palmitate/ascorbic acid, lecithin, or citric acid (Pokorny et al., 2001; Kalsec, 2014a). Liquid mixed tocopherols for use in food are commonly available on the market diluted in a vegetable oil, such as sunflower or soybean oil (Organic Technologies, 2013; Brenntag Specialties, Inc., date unknown). Powdered mixed tocopherols contain a carrier such as tapioca starch, gum acacia, rice maltodextrin, calcium carbonate, or silica (Organic Technologies, 2013; BASF, 2013; Kemin, 2014; NOSB, 1995; BTSA, 2013; BTSA, 2012).

Tocopherols products are commonly formulated with ancillary substances including those listed below:

- Vegetable oil—an agricultural product not specifically named on the National List
- Tapioca starch (also known as tapioca flour)—an agricultural product not specifically named on the National List
- Acacia gum (gum arabic)—an agricultural product generally used as a stabilizer, emulsifier, and thickener in foods; nonorganically produced gum arabic (water extract only) is allowed as an ingredient in or on processed products labeled as "organic" (7 CFR 205.606 [k]); a direct food substance affirmed as GRAS (21 CFR 184.1330)
- Maltodextrin—a synthetic substance derived from a starch, not included on the National List; a direct food substance affirmed as GRAS (21 CFR 184.1444)

[1]Polyunsaturated fatty acids, or polyunsaturated fats, are fat molecules that have more than one double bond in the molecule. Foods high in polyunsaturated fats include plant-based oils. These oils are typically liquid at room temperature, but start to turn solid when chilled. Sources include nuts, seeds, tofu, and soybeans. Polyunsaturated fats can help reduce bad cholesterol levels in the bloodstream (American Heart Association, 2014a).

[2]Saturated fatty acids, or saturated fats, are fat molecules that have no double bonds between carbon atoms. Foods high in saturated fats include animal products such as meat, poultry with skin, lard and cream, butter, cheese, and other dairy products made with whole or 2% milk. Some plant-based oils also have saturated fats (e.g., palm oil, coconut oil). Saturated fats are typically solid at room temperature (American Heart Association, 2014b).

- Calcium carbonate—a nonagricultural, nonsynthetic 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]); a direct food substance affirmed as GRAS (21 CFR 184.1191)
- Silica—also known as silicon dioxide, a nonagricultural synthetic substance allowed as an ingredient in or on processed products labeled as "organic" or ''made with organic (specified ingredients or food group[s])," permitted as a defoamer only; allowed for other uses when organic rice hulls are not commercially available (7 CFR 205.605[b])

Tocopherols may be used in combination with other antioxidants and synergists including those listed below:

- Rosemary extract—an agricultural product not specifically named on the National List
- Ascorbyl palmitate—a synthetic form of vitamin C; not specifically named on the National List
- Ascorbic acid—a nonagricultural, synthetic 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[b])
- Lecithin—an agricultural product generally used as an emulsifier in foods; nonorganically-produced lecithin (de-oiled) is allowed as an ingredient in or on processed products labeled as "organic," (7 CFR 205.606[o]) and is permitted only when an organic form is not commercially available
- Citric acid—a nonagricultural, nonsynthetic 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]) and is permitted only when produced by microbial fermentation of carbohydrate substances

Status

Historic Use:

Tocopherols were first used as antioxidants in food in 1949 (Burdock, 1997). Today, they are used in a variety of processed foods and animal feeds. Synthetic tocopherols have been included on the National List since 2001. The material was first reviewed by the NOSB in 1995 (NOSB, 1995). Tocopherols have been used in cosmetic formulations for many years (CIR, 2002).

Organic Foods Production Act, USDA Final Rule:

Tocopherols (derived from vegetable oil when rosemary extracts are not a suitable alternative) are included on the National List as a synthetic nonagricultural 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[b]).

Mixed tocopherols contain alpha-tocopherol, a form of vitamin E. Nutrient vitamins and minerals (in accordance with 21 CFR 104.20, Nutritional Quality Guidelines For Foods) are included on the National List as synthetic substances allowed as ingredients in or on processed products labeled as "organic" or ''made with organic (specified ingredients or food group[s])'' (7 CFR 205.605[b]). Vitamins and minerals are an allowed category under Section 2118 of the Organic Foods Production Act of 1990 (OFPA).

International:

Canadian General Standards Board (CGSB) Permitted Substances List

Tocopherols and mixed natural concentrates (derived from vegetable oil when rosemary extracts are not a suitable alternative) are included on the Canadian General Standards Board (CGSB) Permitted Substances List as a nonorganic ingredient classified as a food additive (CGSB, 2011). Tocopherols are not specifically permitted by the CGSB for use as antioxidants in organic livestock production. Antioxidants for use in livestock feed must be from nonsynthetic sources (only water, alcohol, and acid and base extracts permitted by the standard) (CGSB, 2011).

The CGSB Organic Aquaculture Standards do not specifically list tocopherols for use as feed additives in organic aquaculture (CGSB, 2012). Antioxidants for use as feed additives must be from nonsynthetic sources (only water, alcohol, and acid and base extracts permitted by CAN/CGSB-32.310 and CAN/CGSB-32.311). Synthetic sources of antioxidants are permitted when legally required.

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

"Tocopherols, mixed natural concentrates" are listed as ingredients of nonagricultural origin that are permitted for use in organically processed plant products by the CODEX Alimentarius Commission (2001). Tocopherols are not specifically permitted for use in organic livestock feed by the CODEX Alimentarius Commission; however, antioxidants from natural sources are allowed.

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

Tocopherol-rich extract (as an antioxidant for fats and oils) is listed as a substance permitted in the European Union for use in the preparation of organic foodstuffs of plant and animal origin (Commission of the European Communities, 2008). "Tocopherol-rich extracts of natural origin used as an antioxidant" are permitted as feed additives in organic livestock production. In addition, all "natural antioxidant substances" are permitted in feed specifically for aquaculture animals (Commission of the European Communities, 2009).

Japan Agricultural Standard (JAS) for Organic Production

"Mix tocopherol" is listed by the Japan Agricultural Standard (JAS) for Organic Production as a substance permitted for use in organically processed foods of plant and animal origin (Japanese Ministry of Agriculture, Forestry and Fisheries, 2012). In the case of processed foods of animal origin, its use is limited to processed meat products. Tocopherols are not specifically listed by the JAS for Organic Production for use in organic livestock production. Feed additives are only permitted for use in organic livestock production if they are natural substances or derived from natural substances without being chemically treated (Japanese Ministry of Agriculture, Forestry and Fisheries, 2012).

International Federation of Organic Agriculture Movements (IFOAM)

"Tocopherols, mixed natural concentrates" are listed by International Federation of Organic Agriculture Movements (IFOAM) as food additives permitted for use in organically processed foods (IFOAM, 2014). Synthetic forms may be used only if organic and natural sources are not available. Tocopherols are not specifically listed by IFOAM for use in organic livestock or aquatic animal production. However, all preservatives (except when used as a processing aid) are prohibited in the diet of organic livestock and aquatic animals (IFOAM, 2014).

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)).

Processes used to manufacture tocopherol products are described by several sources that are summarized here. The conventional methods used to manufacture tocopherols from vegetable oil and vegetable oil byproducts include solvent extraction, chemical treatment, crystallization, complexation, and vacuum or molecular distillation (Torres et al., 2011).

The 1995 Technical Advisory Panel (TAP) Report for Tocopherols, which reviewed the use of tocopherols as a food antioxidant, stated that tocopherols are made via vacuum steam distillation of edible vegetable oil products (NOSB, 1995). The European Food Safety Authority (EFSA) also reported that mixed tocopherols are obtained via vacuum steam distillation of edible vegetable oil products (EFSA, 2008). The raw material used for the manufacturing of tocopherols is reported to be a byproduct of vegetable oil refining (e.g., deodorizer distillate). Common vegetable oils being used include soybean, rapeseed, sunflower, corn, and cottonseed oils. The vegetable oil byproduct undergoes a combination of purification and distillation steps to produce the mixed tocopherols material. The stereochemistry of the tocopherol compounds is reportedly preserved so that the mixed tocopherols are identical to the various forms of tocopherols found in the natural source material (EFSA, 2008).

Burdock (1997) reported that tocopherols are extracted from vegetable oil deodorizer distillate. Deodorizer distillate, obtained from the deodorization process of vegetable oil refining, is a complex mixture containing many compounds including tocopherols, tocotrienols, sterols, esters of sterols, free fatty acids, and mono-, di-, and triglycerides. The other compounds can be separated from tocopherols through a series of steps that may include esterification with a lower alcohol followed by washing and vacuum distillation, or by saponification or fractional liquid-liquid extraction (Burdock, 1997). The tocopherols can be further purified using one or more of the following processes: molecular distillation, extraction, and/or crystallization. The total tocopherol content of the resulting product is usually 30–80% (Burdock, 1997); the remaining product consists of triacylglycerols (the main constituents of vegetable oil) (Pokorny et al., 2001).

In a petition for listing tocopherols on the National List as a synthetic substance allowed for use in organic aquatic animal production, the Aquaculture Working Group indicated that mixed tocopherols are extracted from soybean oil using solvent extraction. The soybean oil is extracted from beans also using solvent extraction. Hexane was reported as a commonly-used solvent, and other solvents may include ethanol, isopropanol, acetone, isopentane, isohexane, trichloroethylene, or petroleum ether (Aquaculture Working Group, 2012; Oreopoulou and Tzia, 2010).

In a 2012 document, EFSA reported that tocopherols are produced from vegetable oils through a series of extraction steps that include crystallization, multiple distillations, and, finally, a standardization of the additive with vegetable oil (EFSA, 2012). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) also reported that a vegetable oil may be added to the purified tocopherols mixture in order to adjust the required amount of total tocopherols in the product (JECFA, 2006). Powdered tocopherol products are produced by spray-drying a liquid tocopherol product onto a carrier or mixture of carriers such as tapioca starch, gum acacia, rice maltodextrin, calcium carbonate, or silica (Organic Technologies, 2013; BASF, 2013; Kemin, 2014; NOSB, 1995; BTSA, 2013; BTSA, 2012).

The Spanish manufacturer BTSA produces Tocobiol®, a mixed tocopherols product, using short path molecular distillation of vegetable oils (BTSA, 2014a). The manufacturer claims that this product is unique because it preserves high levels of the naturally-occurring sterols, squalene and mono-diglycerides, from the vegetable oils and is produced using only physical processes (i.e., no solvents or chemicals are added) (Piñol del Olmo, date unknown).

Alternative methods of manufacturing tocopherols from vegetable oil byproducts have been reported in the literature, including supercritical carbon dioxide extraction that minimizes environmental impact compared with conventional extraction with organic solvents. Although conventional extraction techniques are still widely used to isolate natural products, many industries (e.g. food, pharmaceutical, chemical, and fuel industries) are interested in supercritical fluid extraction as evidenced by numerous scientific papers and patents utilizing this technique (Mendiola et al., 2013). It is unclear if this technique is currently being used to commercially manufacture tocopherols.

Alternative feedstocks for the production of tocopherols have also been reported in the literature and include palm oil, soybean, rice bran, and olive tree leaves (de Lucas et al., 2002). According to Pokorny (2007), natural tocopherol concentrates may be obtained from wheat or corn germ.

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

The available sources indicate that tocopherols for use as antioxidants in food are derived from natural plant sources via chemical and physical processes that are used alone or in combination (Torres et al., 2011). Following the processes used to extract and purify tocopherols, the compounds that remain are in the same form as in the naturally-occurring source plant materials.

Tocopherols are extracted from a natural plant material (vegetable oil) through many different steps. Most of the available sources indicate that a byproduct of vegetable oil refining (deodorizer distillate) is commonly used as the raw material for the manufacturing of tocopherols. Deodorizer distillate is reported to be an important commercial source of tocopherols (Verleyen et al., 2001). Deodorization is the final step in the chemical refining of edible vegetable oils. It is a steam distillation process used to remove undesirable ingredients to produce oil with characteristic mild odor and flavor (Medina-Juarez and Gamez-Meza, 2011). Vegetable oil deodorizer distillate is not an agricultural source marketed for human consumption; however, it is derived from an agricultural source (vegetable oil).

The extraction of tocopherols from vegetable oil byproducts may include one or more of the following chemical processes: esterification, saponification, solvent extraction, and/or crystallization using a solvent (see the response to Evaluation Question #1). Physical separation methods may also be used during the extraction of tocopherols, and these include various distillation steps. At least one manufacturer of a mixed tocopherols product claims to manufacture its product using physical process only. Specifically, the Spanish manufacturer BTSA produces a mixed tocopherols product—Tocobiol®—through short path molecular distillation of vegetable oils, claiming that no solvents or chemicals are added during the manufacturing process (BTSA, 2014a; Piñol del Olmo, date unknown).

Esterification is a chemical process that can be used to prepare the deodorizer distillate for easier separation of the tocopherols. The tocopherol compounds themselves are not meant to be esterified in this step although they may react to a limited extent (Barnicki et al., 1996). Rather, esterification is used to convert the volatile alcohols in vegetable oils into less volatile fatty acid esters (Ogbonna, 2009). The tocopherols can then be separated from the other compounds with different boiling points using distillation at different temperatures. One example of this is explained in U.S. Patent No. 5,512,691 (Barnicki et al., 1996). According to this document, esterification occurs when the distillate is heated under high pressure. An acid may be added as a catalyst (e.g., butyl stannoic acid, zinc acetate, phosphoric acid, dibutyl tin oxide, or other mild mineral acids), and additional C_{10}-C_{22} fatty acids may be added to the solution (Barnicki et al., 1996). Nagao et al. (2005) report that a lipase such as *Candida* sp. lipase may be used as a catalyst during esterification instead of an acid. During the reaction steps, the sterols present in the distillate react with the free fatty acids to form sterol esters; the alcohol moieties react to form fatty acid esters and waxes; and the mono- and di- fatty acid glycerides are converted to triglycerides (Barnicki et al., 1996). The unchanged tocopherols are then separated from these compounds through a series of distillations.

Saponification is another chemical process that can be used to prepare the deodorizer distillate for easier separation of the tocopherols. One example of this is explained in U.S. Patent Application No. US 2008/0015367 A1 (Dobbins et al., 2008). According to this document, the phytosterol fatty acid esters present in the deodorizer distillate can be saponified with potassium hydroxide forming a solvent medium of methanol, water, and the potassium soaps of fatty acids. The tocopherols remain unsaponified and can be recovered via acidification of the mixture with a dilute aqueous solution of a mineral acid followed by separation of the water-immiscible mixture and fractional distillation (Dobbins et al., 2008).

In a petition for listing tocopherols on the National List as a synthetic substance allowed for use in organic aquatic animal production, the Aquaculture Working Group (2012) indicated that mixed tocopherols are extracted from soybean oil using solvent extraction. Hexane was reported as a commonly used solvent, and other solvents may include ethanol, isopropanol, acetone, isopentane, isohexane, and trichloroethylene (Aquaculture Working Group, 2012). Oreopoulou and Tzia (2010) also reported that nonpolar solvents such as hexane and petroleum ether can be used for the extraction of tocopherols.

No sources were identified that discuss whether the synthetic materials used in the extraction of tocopherols remain in the final product in any significant amounts.

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)).

Many of the commercially available mixed tocopherols products are advertised as "natural source" or "natural mixed tocopherols;" however, the available information indicates that these claims are related to the fact that the tocopherol compounds in the products are the same as those occurring in nature, and the products are derived from natural sources (i.e., various vegetable oils). The end products themselves are typically manufactured using chemical processes and are therefore synthetic. Only one manufacturer was identified that claimed its product was manufactured completely by a physical process (short path molecular distillation) without the use of solvents or added chemicals (BTSA, 2014a; Piñol del Olmo, date unknown).

Wheat germ oil extracted by physical means is a natural product that is high in tocopherols. Analyses show that it contains around 1,900 μg/g total tocopherols (<1%) (Herting and Drury, 1963). For comparison, commercially available mixed tocopherols concentrates contain between 30-90% total tocopherols. No sources were found describing the use of wheat germ oil or other natural sources of tocopherols as antioxidants in processed foods.

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.

Tocopherols are affirmed as generally recognized as safe (GRAS) by FDA when used as chemical preservatives (21 CFR 182.3890) or nutrients (21 CFR 182.8890) in food for human consumption in accordance with good manufacturing practice.

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 function of tocopherols in processed foods is a preservative. Tocopherols function as an antioxidant ingredient used for the stabilization of food products that contain lipids (i.e., fats and oil) susceptible to oxidative rancidity. Tocopherols protect food against oxidation reactions caused by free radicals (Shahidi and Wanasundara, 2011) (refer to Action of the Substance section for more detail). This action helps to preserve the taste and nutritional value of the food. Tocopherols are used as an antioxidant preservative in many different food categories including dairy products, cereals, frozen green vegetables, margarine, fresh and frozen sausages, vegetable oils, soft drinks, snacks and nuts, salad dressings, soup bases, seasonings, dehydrated potatoes, processed meats and poultry, and baked products (Shahidi and Wanasundara, 2011).

Tocopherols may also be used as a nutrient (source of vitamin E) in food or supplements for human consumption.

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)).

Tocopherols are not added to foods to recreate or improve flavors, colors, textures, or nutritive values lost in processing. They are used to prevent and delay oxidative rancidity in lipid-containing foods thereby preserving the flavor and nutritional value of the food and increasing its shelf life (Shahidi and Wanasundara, 2011).

<u>Evaluation Question #7</u>: 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)).

Tocopherols have an effect on the nutritional quality of foods because of their antioxidant properties. Mixed tocopherols contain alpha-tocopherol, a form of vitamin E. Tocopherols protect food against oxidation reactions caused by free radicals (Shahidi and Wanasundara, 2011) and this action helps to preserve the taste and nutritional value of the food.

<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 tocopherols. No substances listed on FDA's Action Levels for Poisonous or Deleterious Substances in Human Food have been reported as contaminants of concern in tocopherols.

<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)).

The process to manufacture tocopherols may be harmful to the environment if organic solvents and other chemicals are used. As described in the response to Evaluation Questions #1 and #2, organic solvents and other chemicals may be used in the commercial extraction of tocopherols from vegetable oil. If these chemicals are released into the environment through waste streams, then environmental contamination could occur. No sources were found that discussed environmental contamination resulting from the manufacturing of tocopherols.

It is unlikely that the uses of tocopherols as an antioxidant in human foods or its breakdown products are harmful to the environment or biodiversity. Tocopherols are abundant in plant tissues (DellaPenna and Pogson, 2006) and, therefore, are naturally abundant in the environment. Vitamin E (alpha-tocopherol) is an essential nutrient in the diet of all mammals (DellaPenna and Pogson, 2006).

Tocopherols are easily oxidized in the presence of light or metals or when exposed to high temperatures or alkaline pH conditions (Lampi et al., 2002). Oxidative degradation of tocopherols results in the formation of tocopheroxides, tocopherol quinones, and tocopherol hydroquinones (Gregory, 1996). Further oxidation and rearrangement reactions can lead to the formation of many other compounds. Pokorny (2007) stated that, by reaction with free radicals, tocopherols are converted to quinones, spirodimers, copolymers with oxidized lipids, and various other compounds. Quinones are a group of compounds that are ubiquitous in nature, and they occur naturally in plants, fungi, and bacteria (Monks and Jones, 2002). Tocopherol spirodimer is a major product of tocopherol oxidation in vivo and is found in animal tissues (Al-Malaika, 2004). In conclusion, tocopherols and its breakdown products occur naturally in the environment; therefore, the use of tocopherols as an antioxidant ingredient in food does not raise environmental concerns.

No sources were found that discussed the possible persistence of tocopherols in the environment. Concentrations of tocopherols or its breakdown products in the environment were also not found.

<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)).

It is unlikely that the use of tocopherols as an antioxidant in foods is harmful to human health. Tocopherols are a natural part of the human diet, with a large proportion of intake coming from tocopherols naturally present in vegetable oils (IOM, 2000). Tocopherols are affirmed as GRAS by FDA when used as chemical preservatives or nutrients in food for human consumption in accordance with good manufacturing practice (21 CFR 182.3890, 182.8890). Reports of adverse effects of tocopherols in humans are limited to studies and cases involving supplementation with high levels of alpha-tocopherol, the most biologically active form of tocopherol in humans.

As stated above, tocopherols are a natural part of the human diet. Gamma-tocopherol is the most prominent form present in the American diet (Yang et al., 2012). The various forms of tocopherols are not interconvertible within the human body, and alpha-tocopherol is the only form that has vitamin E activity for humans (IOM, 2000). The Recommended Dietary Allowance (RDA) for vitamin E (as alpha-tocopherol) set by the Institute of Medicine (IOM, 2000) ranges from 6 mg/day for young children to 15 mg/day for adults (19 mg/day for lactating women). The Tolerable Upper Intake Level (UL) for alpha-tocopherol ranges from 200 mg/day for young children to 1,000 mg/day for adults. The UL is the highest level of total daily alpha-tocopherol intake that is likely to pose no risk of adverse health effects in almost all individuals. The UL applies to all stereoisomers of alpha-tocopherol (IOM, 2000).

There is no evidence of adverse effects resulting from the consumption of alpha-tocopherol naturally occurring in foods (IOM, 2000). The National Institutes of Health (NIH) Office of Dietary Supplements reports that, "eating vitamin E in foods is not risky or harmful" (Office of Dietary Supplements, 2011). Excessive intake of alpha-tocopherol in humans from supplementation or pharmacological use might increase the risk of bleeding (by reducing the blood's ability to form clots after a cut or injury) or hemorrhagic stroke (IOM, 2000; Office of Dietary Supplements, 2011). However, a clear causal relationship between alpha-tocopherol and these effects has not yet been established (IOM, 2000). Other side effects of excessive alpha-tocopherol intake have been reported in various studies and include fatigue, emotional disturbances, thrombophlebitis, breast soreness, creatinuria, altered serum lipid and lipoprotein levels, gastrointestinal disturbances, and thyroid effects (IOM, 2000). However, none of these reported effects have been consistently observed in controlled studies.

Meta-analyses that examined high-dosage vitamin E supplementation and increased risk of mortality have had mixed results. Several published meta-analyses have linked high-dosage vitamin E supplementation (above the RDA of 15 mg/day) to small but statistically significant increases in all-cause mortality (i.e., death from any cause) (Miller et al., 2005; Bjelakovic et al., 2007; Bjelakovic et al., 2013). These studies examined mortality data from the large database of clinical trials that have tested vitamin E supplementation as a therapy to prevent various chronic diseases. The causes of the observed increases in mortality were not assessed by the study authors. In contrast to their findings, one recent meta-analysis (Curtis et al., 2014), that included only trials undertaken in highly-developed countries in apparently healthy adults, showed no effect on all-cause mortality with vitamin E supplementation at doses of 23–800 IU/day (equivalent to 15–536 mg/day of natural alpha-tocopherol using conversion factors provided in Office of Dietary Supplements [2013]).

Animal studies have demonstrated that alpha-tocopherol is not mutagenic, carcinogenic, or teratogenic (IOM, 2000); however, some recent research suggests that vitamin E supplementation below the UL (1,000 mg/d in adults) could increase the risk of prostate cancer in men (Office of Dietary Supplements, 2011). A large study supported by NIH concluded that vitamin E supplementation increased the occurrence of prostate cancer by 17% in men who received the vitamin E supplement alone versus those who received a placebo. The vitamin E supplement used in this study was 400 IU/day of all-rac-alpha-tocopherol acetate, which is equivalent to 180 mg/day of natural alpha-tocopherol (using conversion factors provided in IOM, 2000; Office of Dietary Supplements, 2013). No increase in prostate cancer was observed when vitamin E and selenium supplements were taken together (Klein et al., 2011). An update to this study was published in 2014 that examined the effects of vitamin E supplementation on prostate cancer risk conditional upon baseline selenium status of the subjects (Kristal et al., 2014). This new methodology found that vitamin E supplementation alone had no effect among men with high baseline selenium levels, but it did increase the risks of prostate cancer among men with lower selenium levels at baseline. The authors concluded that men should avoid selenium or vitamin E supplementation at doses that exceed recommended dietary intakes (Kristal et al., 2014).

In regard to other forms of tocopherols (beta, gamma, and delta forms), the IOM reports that little information is available on the possible adverse effects to humans resulting from ingestion of amounts of these tocopherols that exceed the levels normally found in foods. A typical mixed tocopherols product consists primarily of gamma-tocopherol, followed by delta- or alpha-tocopherol, with beta-tocopherol representing the lowest proportion in the mixture (CIR, 2002; EFSA, 2008; Organic Technologies, 2013). All forms of tocopherols are absorbed into the body following ingestion; therefore, all forms could contribute to vitamin E toxicity (IOM, 2000). The European Food Safety Authority (EFSA) concluded that the intake of mixed tocopherols from supplement use should be in accordance with the UL for vitamin E of 300 mg/day for adults set by the Scientific Committee on Food (SCF) in 2003 (EFSA, 2008). Recent studies in animals have demonstrated that gamma-tocopherol, delta-tocopherol, and natural mixtures of tocopherols have cancer preventative activity (Yang et al., 2012). A review by cancer prevention researchers (Yang et al., 2012) concluded that "more research on the biologic activities of the different forms and mixtures of tocopherols is needed," and "the possible adverse effects of high doses of tocopherols warrant further investigation."

Vitamin E toxicity may be caused by antagonism with the function of other fat-soluble vitamins (EFSA, 2008). Very high doses of vitamin E in animal studies have shown impaired bone mineralization, reduced liver storage of vitamin A, and hemorrhagic effects. These effects could be corrected in animals by increasing the dietary supplements of the appropriate fat-soluble vitamin (i.e., vitamin D for impaired bone mineralization, vitamin A for reduced liver storage of vitamin A, and vitamin K for hemorrhagic effects) (EFSA, 2008).

No sources were identified that discuss toxic effects resulting from the breakdown products of tocopherols or resulting from contaminants in commercially-produced tocopherols.

<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)).

For some food products, use of an antioxidant such as tocopherols could be avoided by employing one or more of the following approaches: shortening the shelf-life date; reformulating the product; changing the product's packaging or storage/distribution conditions; and/or increasing dietary antioxidants in livestock.

<u>Product Reformulation</u>

One type of product reformulation that can increase the oxidative stability of a food product is to remove or replace the sensitive ingredient(s), such as polyunsaturated oil. The degree of unsaturation of a lipid is one of the most important factors determining the rate of oxidation (Márques-Ruis et al., 2014). The higher the degree of unsaturation, the easier a lipid can become oxidized. As explained in the Action of the Substance section, polyunsaturated fatty acids are the least stable components of lipids (Pokorny, 2007). Therefore, a processed food product made with polyunsaturated oil is highly susceptible to oxidative rancidity. In some cases, replacement of polyunsaturated oil with a less-saturated oil may be an alternative to using an antioxidant in the food product.

In food emulsions, such as mayonnaise, salad dressings, soups, and sauces, higher concentrations of an emulsifier ingredient can increase the oxidative stability of the product (Márques-Ruis et al., 2014). Also, increasing the pH of the emulsion may help to decrease the rate of lipid oxidation (Márques-Ruis et al., 2014).

No sources were identified that compared the effectiveness of product reformulation versus the use of tocopherols as antioxidants in foods.

<u>Packaging Solutions</u>

Active packaging technologies that help to maintain low oxygen content in packages are alternative practices that make the use of antioxidant preservatives unnecessary in some processed foods. These strategies include the use of vacuum packaging, oxygen absorbers, modified atmosphere packs (replacing air by inert packaging gases), antioxidant packaging, enzymes such as glucose oxidase that remove oxygen, and UV-absorbing substances in transparent packaging materials (Saltmarsh and Insall, 2013; Cichello, 2014; Erkmen, 2012; Siró, 2012).

Antioxidant packaging includes antioxidant substances incorporated into packaging systems to provide antioxidant activity. Research has been conducted in different food systems including meat, fish, poultry, cereal, lipids, and lipid products (Tian et al., 2013). Specifically, antioxidant agents can be incorporated into the packaging systems in many different forms, including sachet packages, adhesive-bonded labels, physical adsorption/coating on packaging material surface, packaging polymer matrix, multilayer films, and the food contact packaging surface using covalent immobilization (Tian et al., 2013). Oxygen-scavenging packaging, such as sachets or labels, is the most commercially important category of antioxidant packaging (Tian et al., 2013). Sachets have been successfully used in meat products, bakery products, cheese, nuts, and chips, and oxygen scavenger-containing labels have been successfully used with cooked and cured meat, poultry products, fish, pizzas, and bakery products. Sachets typically contain a metal-based oxygen scavenger, such as iron or iron-based powder. Labels have been made with natural essential oil extracts (e.g., ginger, oregano, cinnamon). Sachets and labels are reportedly not suitable for liquid or high humidity foods (Tian et al., 2013).

No studies were identified that directly compared the effectiveness of active packaging solutions with the use of tocopherols as antioxidants in foods. Some of the commercially available active packaging solutions are described below.

Multisorb Technologies (Buffalo, NY) manufactures oxygen absorber packets, strips, and cards for use in a wide variety of food applications (i.e., baked goods, dairy products, snacks, dried fruits and vegetables, infant formula, and processed meats). According to the manufacturer's website, "Multisorb's active packaging technologies allow natural food formulators to protect their products from the effects of oxidation and moisture loss" thereby reducing the need for preservative ingredients (Multisorb Technologies, 2014a). The packets, strips, and cards contain food grade materials that irreversibly remove oxygen and reduce the oxygen content in the packaging to below 0.01%, which, according to the manufacturer, is significantly less than vacuum packaging and gas flushing (Multisorb Technologies, 2014b).

Wholesale Group International (Australia) manufactures oxygen absorbing satchels made of iron carbonate and activated carbon under the trade name OxySorber™ (Wholesale Group International, 2012).

Changes in Product Storage/Distribution Conditions

The rate of lipid oxidation can be decreased using low-temperature storage (Márques-Ruis et al., 2014). In addition, storage in the dark may also help to delay lipid oxidation in some food products because light acts as a catalyst during the initiation stage of autoxidation (Márques-Ruis et al., 2014). No sources were identified that compared the effectiveness of changing product storage or distribution conditions with the use of tocopherols as antioxidants in foods.

Antioxidant Supplementation in Livestock

In the case of meat products, several researchers have shown that adding antioxidants to the diets of livestock increases the stability of the meat derived from those animals (reviewed in Brewer, 2011). This practice can be an alternative to adding antioxidants to the final meat product. Using this approach, antioxidants are still being used, just at a different stage of food production. Alpha-tocopherol (vitamin E) appears to be a commonly used antioxidant supplement for livestock. Vitamins, used for enrichment or fortification when FDA approved, are allowed as feed additives for use in organic livestock production [7 CFR 205.603(d)(3)].

Several studies that examined antioxidant supplementation in livestock have been conducted. Dietary supplementation with alpha-tocopherol acetate (vitamin E) was shown to have a beneficial effect on the oxidative stability of pork (Boler et al., 2009). Feeding pigs plant extracts containing natural antioxidants was also shown to improve the antioxidant potential of the meat (Lahucky et al., 2010). Adding carnosic acid (an active compound in rosemary extract) or vitamin E to the diets of lambs was shown to increase the oxidative stability of the meat (Morán et al., 2013). Supplementing the diet of cattle with vitamin E plus plant extracts rich in polyphenols effectively protected beef against lipid oxidation (Gobert et al., 2010). Grape pomace concentrate or vitamin E supplementation in the diets of broiler chickens decreased the susceptibility of breast meat to oxidation during refrigerated storage (Brenes et al., 2008). Wheat germ oil used as a source of natural alpha-tocopherol in the diets of broiler chickens was also shown to increase the stability of broiler meat (Arshad et al., 2013).

No studies were identified that directly compared the effectiveness of antioxidant supplementation in livestock diets with the use of tocopherols as antioxidants added to meat products.

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

The suitability of an antioxidant for a particular food application has to be determined on a case-by-case basis because it is difficult to predict the effectiveness of a particular antioxidant in a given food (Pokorny et al., 2001). Factors affecting the choice of antioxidant for a given food include the mechanism of antioxidant activity and chemistry of the food matrix. While there are many natural antioxidants available, they may not be suitable for replacement of tocopherols in a specific food application.

Natural food antioxidants have been the subject of intensive research in recent years (Brewer, 2011). Experiments have been conducted on numerous substances, including spices, herbs, plant extracts (e.g., coffee, tea, grape, wheat), and other plant materials (e.g., various fruits, most parts of olive plant) (Brewer, 2011; Yu et al., 2002; Karre et al., 2013; Taghvaei and Jafari, 2013).

Plant tissues are sources of natural antioxidant compounds including tocopherols, flavonoids, phenolic acids, and carotenoids. These compounds delay autoxidation through several different mechanisms (Brewer, 2011). Tocopherols are sacrificial antioxidants because they donate their phenolic hydrogen atoms to free radicals thereby converting them to stable and nonreactive forms (Hardy and Roley, 2000). Plant extracts that delay autoxidation through similar mechanisms may be suitable replacements for tocopherols if they are effective in the desired food matrix and if they are incorporated at appropriate concentrations.

Spices and herbs often contain high concentrations of phenolic compounds that provide antioxidant protection through a hydrogen donation mechanism—similar to tocopherols—so could be used as alternatives to tocopherols in food products. Examples include phenolic acid compounds that generally act by trapping free radicals and flavonoids that can scavenge free radicals and chelate metals as well. Antioxidative extracts of the *Lamiaceae* family of plants (oregano, marjoram, savory, sage, rosemary, thyme, and basil) have high phenol content. Spices containing high levels of phenolic acids include cinnamon, clove, nutmeg, ginger, turmeric, and black pepper. Garlic, green tea, coffee, and grape extracts also have high phenolic content.

The procedures used to extract natural antioxidants from their plant sources strongly influence the composition and antioxidant activity of the extracts (Brewer, 2011). Also, because plant extracts are aromatic, they may or may not be desirable antioxidant ingredients due to their ability to impart odor or flavor to foods. For example, rosemary extracts can contain verbenone, borneol, and camphor that may impart a rosemary odor to foods (Brewer, 2011). In addition, depending on the types of extraction procedures used, some plant extracts commonly referred to as "natural" by the manufacturer may actually be considered synthetic if chemical processes were used during their manufacture.

Out of the many different natural antioxidants that have been reported in the food science literature, rosemary extract, green tea extract, and grape seed extract appear to be products that are commercially available on a large scale for use as food antioxidants in applications similar to tocopherols. Because all three of these extracts are commercially available in organic forms, they are discussed in more detail below in response to Evaluation Question #13.

<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)).

Organic rosemary extract is a possible alternative for tocopherols in some food applications. Rosemary extracts provide excellent protection in the oxidative stability of lipid matrices (Cordeiro et al., 2013). Rosemary extracts in general are available from many different suppliers around the globe in both liquid and powder forms that are oil or water soluble. Organic rosemary extract is available in liquid form from at least one manufacturer (Mountain Rose Herbs, 2014). According to some of the manufacturers, rosemary extract is suitable for use as an antioxidant in a wide variety of food categories including animal and vegetable fats and oils, margarines and other spreads, potato products, meat, poultry, seafood, baked goods, beverages, snacks, mayonnaise, sauces, salad dressings, cereals, energy bars, nuts, dairy products, fried foods, pasta, marine oils, and flavors (Kemin, 2014a; BI Nutraceuticals, 2014a; DuPont Nutrition and Health, 2014a; FanPharma Co., 2014; Vivita, 2009a; Kalsec, 2014b; Vitablend, 2014). These are similar to the food applications reported for tocopherols (see Specific Uses of the Substance section). Typical usage levels for rosemary extract in foods are 500–2000 ppm (DuPont Nutrition and Health, 2014b), similar to typical usage levels of tocopherols (Lampi et al., 2002; Brenntag Specialties, Inc., date unknown).

Numerous studies have demonstrated the antioxidant activity of rosemary extract in various meat and poultry products (Karre et al., 2013). In general, rosemary products have performed successfully in mechanically deboned turkey meat, vacuum-packaged raw ground beef and pork, cooked pork patties, cooked ground beef, and raw frozen sausage. Some studies in meat products, however, have reported that certain rosemary extracts were ineffective at delaying oxidation (Karre et al., 2013). Karre et al. (2013) postulate that these inconsistencies may be due to differences in the quality of the extracts used in these studies.

Organic green tea extract is another possible alternative for tocopherols in some food applications. Green tea extracts for use as food antioxidants are available from several global suppliers in both liquid and powder forms that are oil or water soluble (Caldic Canada Inc., 2012; Vivita, 2009b; Skyherb Inc., 2014; DuPont Nutrition and Health, 2014a; BI Nutraceuticals, 2014b; MB-Holding GmbH & Co. 2012). Organic forms of green tea extract are available from at least two of those suppliers (Skyherb Inc., 2014; MB-Holding GmbH & Co. 2012). According to some manufacturers, green tea extract is suitable for use as an antioxidant in the following food categories: beverages, dairy products, meat and meat products, snacks, breakfast cereals, energy bars, margarines and spreads, and ready-to-eat meals (MB-Holding GmbH & Co., 2012; Vivita, 2009b; DuPont Nutrition and Health, 2014a). Perumalla and Hettiarachchy (2011) reported that green tea extract has been used in various food applications such as bread, extra virgin olive oil, meat, sausages and fish, dehydrated apple products, rice starch products, and biscuits. Typical usage levels for green tea extract in foods are <500 ppm (DuPont Nutrition and Health, 2014b), similar to typical usage levels of tocopherols (Lampi et al., 2002; Brenntag Specialties, Inc., date unknown).

Organic grape seed extract is also a possible alternative for tocopherols in some food applications. Grape seed extracts for use as food antioxidants are available from several global suppliers in both liquid and powder forms (Naturex, 2014; Skyherb Inc., 2011; Ethical Naturals, Inc., 2014; C.E. Roeper GmbH, 2008). Organic grape seed extract is available from at least one manufacturer (Skyherb Inc., 2014). Perumalla and Hettiarachchy (2011) reported that grape seed extract has demonstrated antioxidant activity alone or in combination with other substances in various food applications such as tomatoes, frankfurters, raw and cooked meat, poultry products, and fish. Typical usage levels for grape seed extract in foods are 100–10,000 ppm (Perumalla and Hettiarachchy, 2011), similar to typical usage levels of tocopherols (Lampi et al., 2002; Brenntag Specialties, Inc., date unknown). The red color and astringent taste of grape seed extract could affect the color and taste of a food product when used at higher concentrations (Perumalla and Hettiarachchy, 2011).

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