Inositol
Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Inositol
cis-1,2,3,5-trans-4,6-Cyclohexanehexol
myo-Inositol; meso-Inositol; iso-Inositol
i-inositol
Hexahydroxycyclohexane
Cyclohexitol

Other Names:
Rat antispectacled eye factor
Mouse antialopecia factor
Inositene; Inositina
Insitolum
Meat sugar
Dambrose

Trade Names:
None Identified

CAS Numbers:
87-89-8 (myo-inositol)
6917-35-7 (non-specific isomer)

Other Codes:
EINECS 201-781-2 (myo-inositol)
EINECS 230-024-9 (non-specific isomer)

Characterization of Petitioned Substance

Composition of the Substance:
Inositol is a 6-carbon, cyclic sugar alcohol that is present in all living cells (Clements and Darnell, 1980). Inositol is mainly present in plants in the form of phytic acid, or inositol hexaphosphate (IP6) (Kirschmann, 2007). However, the inositol in phytic acid and phytic acid salts is generally not bioavailable to humans (Reddy and Sathe, 2002; Montecalvo and Theuer, 1995). In animal cells, inositol is found freely or in the cells' phospholipid membranes in the form of phosphatidylinositol (Pereira et al., 1990; Kirschmann, 2007). While inositol can be present in any of nine structural forms, or stereoisomers, the most stable conformation is myo-inositol (Pereira et al., 1990). The molecular formula for inositol is $C_6H_{12}O_6$; the chemical structures for inositol, phytic acid, and phosphatidylinositol are presented in Figure 1.

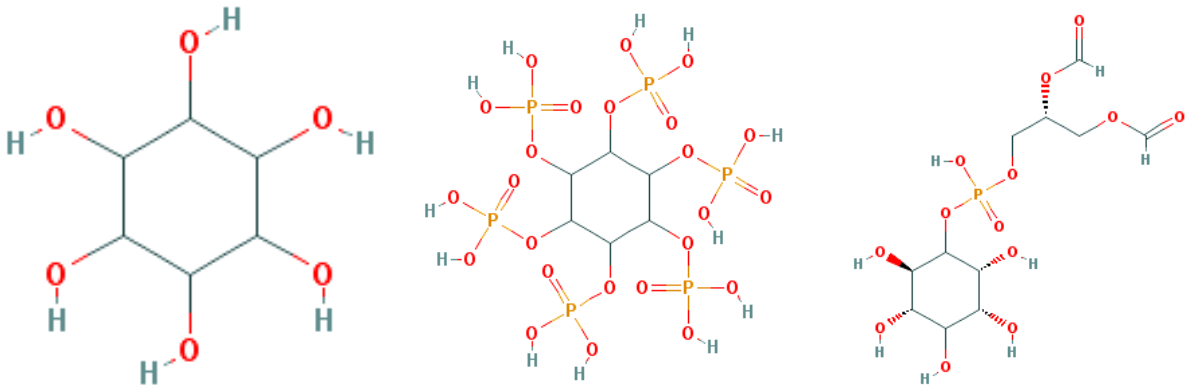

Figure 1. Chemical Structures:
Inositol (left), Phytic Acid (center), Phosphatidylinositol (right)
Source: NLM, 2011b

Properties of the Substance:

Inositol is a white, solid crystalline powder with a molecular weight of 180.16 grams per mole (ScienceLab, 2010). It is very soluble in cold water (ScienceLab, 2010), slightly soluble in alcohol, and insoluble in ether and chloroform (U.S. Pharmacopeia, 2010). The log octanol-water partition coefficient for inositol is less than 1 (NLM, 2011a), indicating that the compound is very hydrophilic (i.e., has a strong affinity for water). Table 1 provides a list of physical and chemical properties of inositol.

Table 1. Physical and Chemical Properties of Inositol

Property	Value
Color	White [2]
Physical State	Solid crystalline powder [2]
Molecular Weight	180.16 g/mol [2]
Melting Point	225 °C [1]
Boiling Point	291 °C [3]
Vapor Pressure	2.05E-09 mm Hg at 25 °C [1]
Solubility	In water: 143 g/L at 19 °C [1]
Octanol/Water Partition Coefficient (log P)	-2.080 [1]
Stability	Stable under normal conditions; instable when exposed to excessive heat, dust generation, or strong oxidizers [2]
Reactivity	Reactivity rating of 0 in HMIS [2]
Flammability/Flame Extension	Flash point: 143.[3] Fire hazard rating of 1 in HMIS and Flammability ranking of 1 in National Fire Protection Agency [2]

[1]NLM, 2011a
[2]ScienceLab, 2010
[3]Chemical Book, 2008

Specific Uses of the Substance:

Inositol is used as a nutritive supplement in infant formula and is available as an over-the-counter nutritional supplement. The petitioned use is as a nutritional supplement to infant formula.

Inositol is traditionally regarded as one of the B vitamins (NLM, 2011a). However, it is not truly a B vitamin but rather works in association with B vitamins, including pyridoxine (B_6), folic acid (B_9), pantothenic acid (B_5), and PABA (B_x) (Kirschmann, 2007). It is also not considered a vitamin because it is biosynthesized at adequate levels within human cells (Navarra, 2004).

Because some forms of inositol (i.e., inositol phosphates, lipid-bound inositol, free inositol) are naturally present in living cells (Clements and Daniel, 1980), it is naturally found in many foods including unprocessed whole grains, some nuts, cantaloupe, most citrus fruits, lima beans, chickpeas, lentils, raisins, and cabbage (Kirschmann, 2007; Conkling and Wong, 2005). It is estimated that Americans consume 1,000 milligrams of inositol daily in their diet (Kirschmann, 2007). This dietary intake is supplemental to the endogenous inositol that is naturally biosynthesized by human cells. Inositol is biosynthesized by cells in many different tissues, including the brain, testis, liver, and especially the kidneys (Carver, 2006). It is commonly found in tissues within the skeletal system, reproductive system, heart, and nerve systems, including large amounts in spinal cord nerves, cerebral spinal fluid, and the brain (Kirschmann, 2007). See "Action of the Substance" for information about the biomolecular role of inositol in the human body. Dietary uptake and endogenous biosynthesis are sufficient to meet the body's inositol requirements (Navarra, 2004), and an inositol deficiency syndrome has not been identified (NLM 2011a). No information was found to indicate that inositol is added to processed foods other than infant formulas for dietary purposes.

Inositol is available as an over-the-counter nutritional supplement (Conkling and Wong, 2005; Kirschmann, 2007), usually in the form of inositol monophosphate, inositol hexaphosphate, or inositol hexaniacinate (Kirschmann, 2007; Conkling and Wong, 2005). No definite dietary need of inositol as a dietary supplement has been established (Navarra, 2004). However, inositol supplements may be recommended by doctors to help lower cholesterol in patients with arteriosclerosis and control neuropathy in diabetics (Conkling and Wong, 2005). Inositol may also play a beneficial role in controlling kidney dysfunction and the inherited metabolic disease galactosemia (Navarra, 2004). Inositol can help eliminate fat from the liver, aid hypoglycemia, lower blood pressure and relieve mild hypertension, treat skin disease such as eczema, treat insomnia and depression, and possibly reduce cholesterol and heart disease (Kirschmann, 2007). Additionally, inositol supplements may be beneficial for infants who born at low weights and with respiratory distress syndrome (Navarra, 2004).

Inositol is present in human breast milk at levels between 1500 uM/L and over 4000 uM/L (Carver, 2006). It is added to infant formulas that are intended to be a replacement for human breast milk, though levels are usually less than 400 uM/L (Carver, 2006). Studies show that serum inositol levels in normal term infants fed human milk are high and decrease over time (Carver, 2006). In preterm (premature) infants fed human milk, serum inositol levels are initially even higher than in term infants, and can even continue to increase for the first few weeks before decreasing (Carver, 2006). Formula-fed preterm infants experience a quicker decline in inositol levels and lower total serum levels than human milk-fed preterm infants (Carver, 2006; Pereira et al., 1990). Concentrations of inositol in serum after birth are influenced by nutritional uptake (Pereira et al., 1990). The role of dietary inositol in infant development is unclear, but studies indicate that inositol may be an important supplement for formula-fed preterm infants (Carver, 2006).

Approved Legal Uses of the Substance:

Inositol does not currently appear on the USDA National List of Allowed and Prohibited Substances (hereafter referred to as the National List) for use in handling/processing of organic food for human consumption.

FDA regulates infant formulas under 21 CFR 107. Non-milk-based infant formulas for sale in the U.S. must contain at least 4 mg inositol per 100 kilocalories to use a nutrient content claim (21 CFR 107.100(a)); however there is no maximum level prescribed in this regulation. The formula label must list the amount of inositol in milligrams per 100 kilocalories of formula, except when it is not added to milk-based formulas (21 CFR 107.10).

Inositol is listed as affirmed as Generally Recognized as Safe (GRAS) for human consumption by the U.S. Food and Drug Administration (FDA) under 21 CFR 184.1370, when used as a nutrient supplement, an ingredient for special dietary foods, or in infant formulas in accordance with good manufacturing practices.

Inositol can be used legally as a human dietary supplement, but it is not registered with the FDA for this use. The FDA does not regulate human dietary supplements in the same way as drugs or animal feed additives; generally, manufacturers do not need to register their products with FDA or get approval before producing and selling supplements for human consumption. The product manufacturer is responsible for ensuring the safety of the product. FDA is responsible for taking action regarding an unsafe product after it reaches the market and to make sure the supplement's label is accurate and not misleading (FDA, 2005).

Action of the Substance:

The human body converts about 7 percent of inositol into glucose and excretes a very small amount (average excretion is 37 milligrams, while average dietary intake is 1000 milligrams) (Kirschmann, 2007). Inositol taken in through the diet or biosynthesized within the body is used to support a variety of the body's cellular needs. Inositol supports cell membrane structure and integrity, and is important for muscle function and cell growth especially in the bone marrow, eye membranes, and intestines (Kirschmann,

2007). Inositol and its phosphate-derivatives function as transmembrane signal mediators, activators of cell surface enzymes, growth factors, and promoters of lipid synthesis (Carver, 2006). Within the body, inositol may function as an antioxidant—for example, studies of laboratory animals have shown that myo-inositol can prevent copper-induced oxidative stress (Jiang et al., 2011).

The role of dietary inositol in infant development is unclear (Carver, 2006), and therefore its action when used as an ingredient in infant formula is uncertain. Inositol has been known to prevent fat accumulation in the liver and intestines, and control triacyglycerol and esterified cholesterol levels; however, neonatal animals fed inositol-depleted diets did not experience effects indicative of fat accumulation in the liver or intestines, suggesting that newborns can maintain proper cellular function despite dietary inositol deficiency (Carver, 2006).

Combinations of the Substance:

Inositol is petitioned for addition to organic infant formula. Organic infant formula contains a number of nutrients (e.g., riboflavin, niacin, pantothenic acid, iodine, copper, potassium) included on the National List (7 CFR 205.605), which identifies nutrient vitamins and minerals allowed for use in organic products as those in the FDA Nutritional Quality Guidelines for Food (21 CFR 104.20(d)(3)). The NOP recently published a proposed rule that would amend the National List reference to 21 CFR 104.20. In particular, the proposed amendment would specify that vitamins and minerals are allowed in organic infant formula as required by 21 CFR 107.100 or 107.10 (USDA, 2012), which is FDA's regulatory standard for infant formula (discussed previously under "Approved Legal Uses of the Substance").

A mixture of food ingredients comprising carbohydrates, proteins, fats, and stabilizers are expected to be included in infant formula to which inositol is added. These ingredients vary with the type of product and manufacturer.

Status

Historic Use:

Inositol was discovered more than 100 years ago when it was identified in the urine of diabetics. In 1941, scientists Gavin and McHenry discovered the metabolic actions of inositol in rats (Navarra, 2004). Commercial manufacture of inositol began prior to 1920 (Eitel, 1920).

It is unclear when inositol was first added to infant formulas. The earliest identified record of inositol in infant formula is a patent for a specific formula composition which was filed in 1980. The patent stated that 23 mg of inositol is added per 100 g of product, as a vitamin (U.S. Patent 4282265). Another patent issued for infant formula in 1987, which gave an example of appropriate nutrient content for infant formula for pre-term infants, listed 10 milligrams of inositol per 100 milliliters of complete formula (U.S. Patent 4670285).

The use of inositol in organic handling has involved some uncertainty due to its nutritional status. Because it is neither a vitamin nor a mineral, there are conflicting opinions regarding its necessity in human nutrition. In 1995, the NOSB wrote "The Use of Nutrient Supplementation in Organic Foods" for the Secretary of the USDA, which stated (USDA, 2011):

> *Upon implementation of the National Organic Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic must be limited to that which is required by regulation or recommended for enrichment and fortification by independent professional associations.*

The NOSB clarified that the term "accessory nutrients" meant "nutrients not specifically classified as a vitamin or a mineral but found to promote optimum health." However, confusion arose after the National List was established because an additional annotation (7 CFR §205.605(b)) stated, "Nutrient Vitamins and Minerals, in accordance with 21 CFR 104.20, Nutritional Quality Guidelines for Foods, would be allowed

for organic agriculture (USDA, 2011)." Originally, the NOP interpreted that under 21 CFR 104.20(f), which states, "Nutrient(s) may be added to foods as permitted or required by applicable regulations established elsewhere in this chapter," inositol and other nutrients not specifically listed in the regulation were permissible. However, after further discussion with the FDA, a memorandum (USDA, 2010) from NOP to the NOSB clarified that 21 CFR 104.20(f) pertained only to substances listed in 21 CFR 104.20(d)(3), which does not include inositol. The NOP recently published a proposed rule that would amend the National List cross-reference to the FDA regulation 21 CFR 104.20, and specify that inositol is allowed in non-milk based infant formulas as required by 21 CFR 107.100 (USDA, 2012). See "OFPA, USDA Final Rule" for more information.

Inositol is currently used in many milk-based and non-milk-based organic infant formulas marketed in the U.S. For example, inositol is used in Vermont Organics™ Infant Formulas (soy-based and milk-based), Similac® Organic Infant Formula, Baby's Only Organic® Soy Formula, and Parent's Choice™ Organic Infant Formula (Vermont Organics, 2012; Abbott Laboratories, 2012; Nature's One, Inc., 2012; Parent's Choice Infant Formula, 2012,).

OFPA, USDA Final Rule:

Inositol is not specifically addressed in the OFPA or the NOP Final Rule (i.e., it is not specifically included on the National List). However, the National List does allow synthetic vitamins and minerals in livestock feed,

> "*Vitamins, used for enrichment or fortification when FDA approved*" (7 CFR 205.603(d)(3))

and in or on processed products,

> "*Nutrient vitamins and minerals, in accordance with 21 CFR 104.20, Nutritional Quality Guidelines For Foods*" (7 CFR 205.605(b)).

There has been confusion over the interpretation of 7 CFR 205.605(b) with regard to certain nutritive supplements. Currently the allowed "vitamins and minerals" do not include several nutrients considered important in specific foods (e.g., infant formula), such as arachidonic acid (ARA) single-cell oil, docosahexaenoic acid (DHA) algal oil, sterols, taurine, choline, and inositol. Inositol, for example, is not currently listed under 21 CFR 104.20 as a nutrient that may be appropriately added to a food to correct a dietary insufficiency, and is not currently considered a vitamin or essential nutrient (Kirschmann, 2007; Navarra, 2004). To clarify this situation, the NOP published a proposed rule in January 2012 (77 FR 1980) that would amend 7 CFR 205.605(b)) as follows:

> ''*Vitamins and minerals. For food – vitamins and minerals identified as essential in 21 CFR 101.9. For infant formula – vitamins and minerals as required by 21 CFR 107.100 or 107.10.*''

If promulgated as a final rule, this amendment would clarify that inositol is allowed in organic-labeled non-milk based infant formulas, because it is required by 21 CFR 107.100.

International:

The International Federation of Organic Agriculture Movements (IFOAM) does not specifically list inositol within its "Norms for Organic Production and Processing" (IFOAM, 2006). However, the IFOAM Norms state that, "Minerals (including trace elements), vitamins and similar isolated ingredients shall not be used unless their use is legally required or where severe dietary or nutritional deficiency can be demonstrated" (IFOAM, 2006).

The Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme also does not list inositol within their guidelines for organically produced foods (Codex Alimentarius Commission, 2001). Minerals (including trace elements), vitamins, essential fatty and amino acids, and other nitrogen

compounds are permitted for use as food additives in organic processed foods only when their use is legally required in the food products in which they are incorporated (CODEX Alimentarius Commission, 2001). The Codex world-wide standard for infant formula states that ready-for-consumption formula must contain a minimum of 4 mg inositol per 100 kilocalories formula. The standard recommends an upper level of 40 milligrams per 100 kilocalories formula (CODEX STAN 72-1981).

Inositol is not specifically listed as a substance permitted for use in organic production by the Canadian General Standards Board (CGSB, 2011). Canadian Food and Drug Regulations do not require infant formula to contain inositol (Section B.25.054 of the Food and Drug Regulations: Health Canada, 2011).

The European Economic Community (EEC) Council Regulations do not list inositol as allowable for use in organic foods/food production (Commission of the European Communities, 2008). While minerals (trace elements included), vitamins, amino acids, and micronutrients are allowed in the processing of organic food, they are only authorized if their use is legally required in the foodstuffs in which they are incorporated (Commission of the European Communities, 2008). For example, European regulations state that ready-to-use or reconstituted infant formula containing soy must contain at least 4 mg inositol (and no more than 40 mg inositol) per 100 kilocalories (Commission Directive 2006/141/EC: Commission of the European Communities, 2006).

The East African Organic Product Standard and the Pacific Organic Standard were both created using the IFOAM and Codex guidelines as models; both standards do not list inositol as allowed for use in organic foods (East African Community, 2007; Secretariat of the Pacific Community, 2008). The Japanese Agricultural Standard for Organic Processed Foods (Japanese MAFF, 2006) do not list inositol.

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)).

Commercial production of inositol follows a two-step process in which (1) phytic acid is extracted from plants, such as corn or rice, and (2) one of several chemical processes is used to transform the phytic acid into inositol. Common manufacturing processes described by the petitioner are described by U.S. Patents 2,112,553 (1938) and 2,414,365 (1947).

In the first step, a calcium-magnesium salt of phytic acid, referred to as phytin, is extracted from a vegetable material by soaking in a dilute acid solution, such as hydrochloric acid or sulfuric acid, and then purified using filtration or another mechanical separation technique followed by precipitation using an alkali reagent (e.g., Ca(OH)2, NaOH, Na_2CO_3, $(NH_2)_2CO_3$), and additional mechanical separation (e.g., filtration, sedimentation) (U.S. Patent 2,112,553). Seeds and grains such as corn, wheat, and oats are good sources of phytin usable for commercial inositol production (U.S. Patent 2,112,553). Inositol is commonly produced from corn steep water, which is the water used to steep corn in order to soften the corn kernel during wet-milling, for various industrial purposes such as production of corn starch, corn syrup, or ethanol fuels (Dang, 2010). Corn steep water typically contains a dilute (1%) sulfurous acid solution, and so the steeping of corn results in phytin released into the water. Inositol can also be produced from defatted rice bran, which is the primary vegetable material used by Tsuno Rice Fine Chemicals Co., Ltd., one of the two inositol manufacturers identified by the petitioner.

For the second step, one of the several possible methods may be used to transform the extracted phytin into inositol. In one of these, the phytin is hydrolyzed with a strong (approximately 30%) sulfuric acid solution and steam pressure. The product of this reaction is a solution mixture that contains inositol, calcium or magnesium sulfate, sulfuric acid and phosphoric acid. The inositol must therefore be separated and purified, which can be done through precipitation using an alkaline reagent like barium, and then

removing the barium using carbonation. This method was the only method for commercial inositol production prior to 1938 (U.S. Patent 2,112,553).

Another method for preparing inositol from phytin, described by U.S. Patent 2,112,553 in 1938, uses water pressure to hydrolyze the phytin without the addition of sulfuric acid solutions. The hydrolysis results in a mixture of inositol, calcium phosphates, and magnesium phosphates. The inositol can be separated by diluting the solution with water, boiling, and then agitating the solution so that the phosphates remain in an insoluble sludge and the inositol remains in solution (U.S. Patent 2,112,553).

Finally, inositol can be prepared from phytin using ammonium salts, such as ammonium sulfate, ammonium chloride, ammonium nitrate, ammonium acetate, or ammonium phosphate, for hydrolysis under conditions of pressure (U.S. Patent 2,414,365). Inositol is then recovered from the hydrolysis mixture using the methods above. Alternatively, the hydrolysis mixture can be diluted with water and calcium oxide, treated with decolorizing charcoal, and filtered. The inositol can then be precipitated, washed, and concentrated using ethyl alcohol (ethanol) and glacial acetic acid (U.S. Patent 2,414,365).

An alternative inositol production method involves recovery of the chemical from yeast cultures, which naturally produce and excrete inositol in the desired, unphosphorylated form (see U.S. Patents 5,618,708; 5,599,701; 5,296,364 and European Patent 506289). As of 1997, a commercial-scale process for inositol recovery from yeast cultures had not been developed (U.S. Patent 5,618,708); no information was found to indicate that this has changed in recent years.

Evaluation Question #2: Is the substance synthetic? 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)).

The petitioned substance can be considered synthetic because the most prevalent commercial production processes involve synthetic steps, as described below and under Evaluation Question #1. As discussed under Evaluation Question #3, nonsynthetic production methods are not available for use on a commercial scale.

Inositol is synthetic because it is industrially manufactured using chemical processes, namely acid reactions and hydrolysis. While inositol ($C_6H_{12}O_6$) is plant-derived, the substance contained within the plant is phytic acid, also known as inositol-hexaphosphate ($C_6H_{18}O_{24}P_6$, or $C_6H_6O_6(PO_3H_2)_6$). Phytic acid is converted to phytin, also known as inositol-hexaphosphate salt ($C_6H_6O_{24}P_6$ $[Ca^{2+}]_5$ $[Mg^{2+}]$, or $C_6H_6O_6(PO_3H_2)_6$ $[Ca^{2+}]_5$ $[Mg^{2+}]$), through the use of acid-base reactions that occur when the vegetable material is soaked in a dilute acid solution and then an alkali is used to precipitate the substance. Then, phytin is converted to inositol through another chemical reaction, hydrolysis. In this reaction, the phosphate groups are cleaved from the molecule and replaced with hydrogen to form a mixture that contains inositol ($C_6H_{12}O_6$) and calcium and magnesium phosphates (PO_4H $[Mg^{2+}]$ and PO_4H $[Ca^{2+}]$). While inositol is plant-derived, it is not an unmodified plant extract.

Evaluation Question #3: Provide a list of non-synthetic or natural source(s) of the petitioned substance (7 CFR § 205.600 (b) (1)).

Some forms of inositol (i.e., inositol phosphates, lipid-bound inositol, free inositol) are naturally found in many foods including unprocessed whole grains, nuts, cantaloupe, citrus fruits, lima beans, chickpeas, lentils, raisins, and cabbage (Kirschmann, 2007; Conkling and Wong, 2005). Inositol is naturally present in human breast milk (Ogasa, 1975; Carver, 2006; Pereira et al., 1990).

An alternative inositol production method involves recovery of the chemical from yeast cultures, which naturally produce and excrete inositol in the desired, unphosphorylated form (see U.S. Patents 5,618,708; 5,599,701; 5,296,364 and European Patent 506289). Yeast is currently included on the National List under 7 CFR 205.605(a) as a non-agricultural, non-synthetic substance allowed for use in processed foods labeled as organic or made with organic ingredients. As of 1997, a commercial-scale process for inositol recovery

from yeast cultures had not been developed (U.S. Patent 5,618,708); no information was found to indicate that this has changed in recent years. Additionally, three out of four patents identified specifically called for the use of a genetically engineered/genetically modified strain of yeast (U.S. Patents 5,599,701; 5,296,364 and European Patent 506289). In general, use of genetic engineering is prohibited in organic production and handling (7 CFR 205.105(e)). The fourth identified patent described a process by which microorganisms of the genus Candida, such as *Candida boidinii,* which are naturally capable of producing and extracellularly secreting inositol, are cultured in a medium and then the accumulated inositol is recovered from the medium (U.S. Patent 5,618,708). Inositol produced in this manner could be considered of a non-synthetic or natural source.

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. What is the technical function of the substance?

Inositol is listed as GRAS for human consumption under 21 CFR 184.1370, under the condition that it is used according to FDA's good manufacturing practices. A review of inositol was completed in 1975 by the Select Committee on GRAS Substances (SCOGS) (U.S. FDA, 2006). The Committee concluded that there was "no available information" on the listed substances "that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future" (U.S. FDA, 2006). The technical function of inositol under 21 CFR 184.1370 is a nutrient supplement.

Evaluation Question #5: Describe whether the primary function/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 function of inositol is not as a preservative. The primary function of inositol is as a nutrient (U.S. Pharmacopeia, 2010).

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)).

No information was found to indicate that inositol is used to recreate or improve flavors, colors, textures, or nutritive values lost during processing. While inositol may provide a nutritional benefit, it is not added to foods to replace or recreate a nutritive value that was lost due to processing of the food. No information was found to indicate that inositol is currently added to processed foods other than infant formula.

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)).

Inositol is marketed as a dietary supplement and is added to infant formula for nutritional purposes. Inositol is traditionally regarded as one of the B vitamins (NLM, 2011a). However, as discussed in the Specific Uses of the Substance section of this report, it is not truly a B vitamin but does work in association with B vitamins, including pyridoxine (B_6), folic acid (B_9), pantothenic acid (B_5), and PABA (B_x) to support a number of biological functions (Kirschmann, 2007). Therefore, inositol has a nutritional role in the body.

When marketed as a dietary supplement pill, it is intended to provide a health benefit, such as lowering blood pressure, cholesterol, and/or heart disease (Kirschmann, 2007), as previously discussed in the Specific Uses of the Substance section. Similarly, inositol is added to infant formula for nutritional reasons. While the dietary role of inositol in infant development is unclear, inositol is present in human breast milk at high levels, and so is added to infant formula (albeit at low levels compared to the amount in human milk) that is intended to mimic and replace human breast milk in an infant's diet (Carver, 2006). It has

been shown that concentrations of inositol in serum are influenced by nutritional uptake (Pereira et al., 1990) and so the addition of inositol to infant formulas may be important for infant health (Carver, 2006).

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

No reports of excessive levels of heavy metals or other dangerous contaminants in inositol have been identified, and no substances listed on FDA's Action Levels for Poisonous or Deleterious Substances in Human Food have been reported as contaminants of concern for inositol. The specifications for inositol in the seventh edition of the "Food Chemicals Codex" include that it contain no more than 4 mg/kg lead, 0.005% chloride, and 0.006% sulfate. Calcium content must be low enough that addition of 1 mL ammonium oxalate to a 10 mL sample of the inositol (at a 100 mg/mL concentration) results in a solution that remains clear for at least 1 minute (U.S. Pharmacopeia, 2010).

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

No information was found to indicate that the manufacture and/or use of inositol may be harmful to the environment or biodiversity. Production of inositol from corn steep water requires energy, in the form of steam and pressure.

Inositol is produced from corn steep water, a by-product of wet-milling of corn to produce corn-based products ranging from corn syrup and corn starch to corn-based ethanol fuel (Dang, 2010). Production of inositol from corn steep water may be considered environmentally beneficial, because a waste by-product is utilized as a feedstock in place of virgin plant material.

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

No information was found to indicate that use of inositol may have adverse human health effects. Because inositol is a nutrient, positive health effects are expected to result from its use. As discussed in the Specific Uses of the Substance section, inositol may help lower cholesterol in patients with arteriosclerosis and control neuropathy in diabetics (Conkling and Wong, 2005). Inositol may also play a beneficial role in controlling kidney dysfunction and the inherited metabolic disease galactosemia (Navarra, 2004). Inositol can help eliminate fat from the liver, aid hypoglycemia, lower blood pressure and relieve mild hypertension, treat skin disease such as eczema, treat insomnia and depression, and possibly reduce cholesterol and heart disease (Kirschmann, 2007). Additionally, inositol supplements may be beneficial for infants who born at low weights and with respiratory distress syndrome (Navarra, 2004).

Evaluation Information #11: Provide a list of organic agricultural products that could be alternatives for the petitioned substance (7 CFR § 205.600 (b)(1)).

Consumption of organic foods that contain inositol, such as unprocessed whole grains, nuts, cantaloupe, citrus fruits, lima beans, raisins, and cabbage, could be considered an alternative to the use of foods supplemented with synthetic inositol.

Inositol is naturally present at high levels in human breast milk (Carver, 2006) and at lower levels in various animal milks (for example, one study measured 10.6 mg/100mL in cow's milk compared to 32.7 mg/mL in human milk) (Ogasa et al., 1975). An alternative to inositol supplemented infant formulas might be organic cow milk-based formulas. However, the inositol intake by infants fed milk-based formulas without added inositol is substantially lower than the inositol intake by infants fed human breast milk (Carver, 2006; Pereira et al., 1990). Further, adverse reactions to cow's milk are common in infants (Kvenshagen et al., 2007), so suitable alternative nutrition sources must be available.

References:

Abbott Laboratories. 2012. Similac® Organic. Retrieved January 25, 2012 from http://abbottnutrition.com/products/similac-organic.

Carver, J. 2006. Ch. 19: Conditionally essential nutrients: Choline, inositol, taurine, arginine, glutamine, and nucleotides. In Thureen, P.J., Hay, W. W. (Eds). Neonatal Nutrition and metabolism (Second Edition). Cambridge University Press, New York, NY.

Chemical Book. 2008. 1,2,3,4,5,6-Cyclohexanehexol (87-89-8). Retrieved November 10, 2011 from http://www.chemicalbook.com/ProductMSDSDetailCB0332590_EN.htm.

Codex Alimentarius Commission. 2001. Guidelines for the production, processing, labeling and marketing of organically produced foods (GL 32 – 1999, Rev. 1 – 2001). Joint FAO/WHO Food Standards Programme. Available online at http://www.fao.org/organicag/doc/glorganicfinal.pdf.

Commission of the European Communities. 2006. Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae amending Directive 1999/21/EC. Official Journal of the European Union. Available online at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:401:0001:0033:EN:PDF.

Commission of the European Communities. 2008. Commission Regulation (EC) No 889/2008 of 5 September 2008 laying down detailed rules for the implementation of Council Regulation (EC) No 834/2007 on organic production and labelling of organic products with regard to organic production, labelling and control. Official Journal of the European Union. Available online at http://www.organic-world.net/35.html?&tx_ttnews[tt_news]=111&cHash=b1bc05316718066deadd4c1f9e54549d.

Conkling, W., Wong, D.Y. 2005. The Complete Guide to Vitamins, Herbs, and Supplements: The Holistic Path to Good Health. Avon Books, Harper Collins Publishers. New York, NY.

Dang, J. 2010. An integrative approach for phytate degradation and recovery of myo-inositol and phosphate as value-added products from the by-products of corn ethanol industry. Dissertation presented to the faculty of the Graduate College at the University of Nebraska, in partial fulfillment of requirements for the degree of Doctor of Philosophy, Chemical and Biomolecular Engineering. Available online at http://digitalcommons.unl.edu/chemengtheses/7/

East African Community. 2007. East African organic products standards. EAS 456:2007. Available online at http://www.ifoam.org/partners/projects/pdfs/EAS%20456-2007_Organic%20products%20standard_w_cover.pdf

Eitel, E. H. 1920. American progress in the bacteriological sugars. The journal of industrial and engineering chemistry, 12(12): 1202-1205.

CGSB (Canadian General Standards Board). 2011. Organic Production Systems Permitted Substances List. CAN/CGSB-32.311-2006. Amended October 2008, December 2009 and June 2011. Available online at http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/internet/bio-org/index-eng.html

Health Canada. 2011. Section B.25.054(1)(a)(vii) of the Food and Drug Regulations. Available online at http://lois-laws.justice.gc.ca/eng/regulations/C.R.C.,_c._870/page-172.html

IFOAM (International Federation of Organic Agriculture Movements). 2006. The IFOAM Norms for Organic Production and Processing. Version 2005. Corrected version 2009. Available online at http://www.ifoam.org/about_ifoam/standards/norms/norm_documents_library/norms_documents_library.html.

Japanese MAFF (Ministry of Agriculture, Forestry and Fisheries). 2006. Japanese Agriculture Standard for Organic Plants (Notification No. 1180 of 2009). Established: Notification No. 59 of January 20, 2000. Partial revision: Notification No. 1884 of November 18, 2003. Full revision: Notification No. 1605 of October 27, 2005. Partial revision: Notification No. 1463 of October 27, 2006. Partial revision: Notification No. 1180 of August 20, 2009. Available online at http://www.maff.go.jp/e/jas/specific/criteria_o.html

Jiang, W.D., Wu, P., Kuang, S.Y., Liu, Y., Jiang, J., Hu, K., Li, S.H., Tang, L., Feng, L., Zhou, X.Q. 2011. Myo-inositol prevents copper-induced oxidative damage and changes in the antioxidant capacity in various organs and the enterocytes of juvenile Jian carp (Cyrpinus carpio var. Jian). Aquatic Toxicology 105(3-4): 543-551. http://www.ncbi.nlm.nih.gov/pubmed/21924699

Kirschmann, J.D. 2007. Nutrition Almanac. Sixth Edition. Nutritional Search, Inc., McGraw-Hill. New York, NY.

Montecalvo, J.; Theuer, R. 1995. Technical Advisory Panel Report for Nutrient Vitamins. Available online at http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5067006&acct=nopgeninfo.

Nature's One, Inc. 2012. Baby's Only Organic® soy formula. Retrieved January 25, 2012 from http://www.naturesone.com/soy/.

Navarra, T. 2004. The encyclopedia of vitamins, minerals, and supplements. Second Edition. Facts on File, Inc., Infobase Publishing. New York, NY.

NLM. 2011a. ChemIDplus Lite – Inositol. TOXNET, Toxicology and Environmental Health Information Program, U.S. National Library of Medicine, Bethesda, MD. Retrieved November 30, 2011 from http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp.

NLM. 2011b. PubChem Compound Summary – Inositol. National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda, MD. Retrieved November 30, 2011 from http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=892&loc=ec_rcs.

Ogasa,K., Kuboyama, M., Kiyosawa, I., Suzuki, T., Itoh, M. 1975. The content of free and bound inositol in human and cow's milk. J Nutr Sci Vitaminol (Tokyo) 21(2): 129-135.

Parent's Choice. 2012. Parent's Choice organic infant formula. Retrieved January 25, 2012 from http://www.parentschoiceformula.com/organic-baby-formula.aspx.

Pereira, G.R., Baker, L., Egler, J., Corcoran, L., Chiavacci, R. 1990. Serum myoinositol concentrations in premature infants fed human milk, formula for infants, and parenteral nutrition. American Journal of Clinical Nutrition, 51: 589–593.

Reddy, N.R. and Sathe, S.K (Eds). 2002. Food Phytates. CRC Press: Boca Raton, FL. 258 pp.

ScienceLab. 2010. Inositol MSDS. Retrieved November 10, 2011 from http://www.sciencelab.com/msds.php?msdsId=9924370

Secretariat of the Pacific Community. 2008. Pacific Organic Standard. Available online at http://www.ifoam.org/partners/projects/pdfs/Pacific_Organic_Standard.pdf

U.S. Pharmacopeia. 2010. 2010-2011 Food Chemicals Codex. Seventh Edition. The United States Pharmacopeial Convention, Rockville, MD.

USDA (U.S. Department of Agriculture). 2010. Action memorandum for the chairman of the National Organic Standards Board: Scope of nutrient vitamins and minerals in organic food. Retrieved January 24, 2012 from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5084068&acct=nosb.

USDA (U.S. Department of Agriculture). 2011. Proposed recommendation: The use of nutrient supplementation in organic foods. National Organic Standards Board, Handling Committee. Retrieved January 24, 2012 from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5089716&acct=nosb.

USDA (U.S. Department of Agriculture). 2012. Proposed Rule: National Organic Program (NOP); Sunset review (2012) for nutrient vitamins and minerals. FR 77(8):1980-1996. Retrieved February 6, 2012 from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5096390.

U.S. FDA (Food and Drug Administration). 2006. (database). Database of Select Committee on GRAS Substances (SCOGS) Reviews. Last updated 10/31/2006. Accessed on December 1, 2011. Available online at http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=scogsListing

U.S. FDA (US Food and Drug Administration). 2005. Dietary supplements. Retrieved January 25, 2012 from http://www.fda.gov/food/dietarysupplements/default.htm.

Vermont Organics. 2012. Organic infant formulas. Retrieved January 25, 2012 from www.vermontorganicsformula.com.