L-Carnitine
Handling/Processing

Identification of Petitioned Substance

Chemical Names:
1-Propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl-, hydroxide, inner salt
3-Carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt
3-hydroxy-4-(trimethylazaniumyl)butanoate
β-hydroxy-γ-trimethyl-amino-butyric acid

Other Names:
L-Carnitine
Carnitine
Levocarnitine

Trade Names:
Carnitor® SF
Carnovis
L-Carnitine-300
Carnipure

CAS Number:
541-15-1

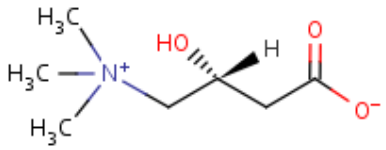
Other Codes:
BP2980000 (RTECS number)
208-768-0 (EINECS number)

Characterization of Petitioned Substance

Composition of the Substance:

Carnitine is a quaternary ammonium compound that is synthesized in the body from the amino acids lysine and methionine (Rebouche, 1992). Carnitine is found as two stereoisomers—L-carnitine and D-carnitine—which have the same molecular formula ($C_7H_{15}NO_3$), but different three-dimensional shapes. L-carnitine is the biologically active isomer. L-carnitine is naturally found at relatively high concentrations in certain foods such as red meat, beans, and avocado. However, depending upon diet, age, and other factors, supplementation of carnitine may be needed to maintain adequate levels in the body (Lango et al., 2001). The molecular structure of L-carnitine is provided as Figure 1.

Figure 1. Molecular Structure of L-Carnitine



Source: ChemIDplus Lite (2012)

Properties of the Substance:

L-carnitine is a white crystalline, hygroscopic (moisture-retaining) powder. It is available commercially as oral L-carnitine; intravenous (iv) L-carnitine, acetyl-L-carnitine, or propionyl-L-carnitine; and the salts L-carnitine HCl, L-carnitine tartrate, and L-carnitine fumarate (HSDB, 2008). It is readily soluble in water and hot alcohol, but almost insoluble in acetone, ether, and benzene. Physical and chemical properties of L-carnitine are summarized in Table 1.

Table 1. Physicochemical Properties of L-Carnitine

Physical or Chemical Property	Value[a]
Physical state	Solid
Appearance	White crystalline, hygroscopic powder
Odor	Characteristic
Molecular weight (g/mol)	161.2
Boiling point	ND
Melting point	197°C
Solubility in water (mg/L)	1.0×10^6 at 25°C
Vapor pressure (hPa)	ND
Density (g/cm^3)	ND

[a]Sources: ChemIDplus Lite (2012); HSDB (2008)
ND = no data

Specific Uses of the Substance:

While it is not an amino acid, L-carnitine is an important compound in human metabolism because it facilitates the entry of long-chain fatty acids, necessary for energy generation, into mitochondria. It is considered "conditionally essential" because some humans, including infants, are unable to synthesize the compound endogenously at adequate levels (Rebouche, 1992). L-carnitine is available as a supplement to treat carnitine deficiency and as a therapeutic treatment for various ailments such as myocardial injury after ischemia (a condition in which there is restricted blood supply to tissues). It is available in many forms, including capsule, injection, liquid, solution, and tablet forms (HSDB, 2008). It is also provided as a supplement in infant formulas, particularly in soy-based formulas that contain very low levels of carnitine when unsupplemented.

Although L-carnitine is present in cow's milk, the petitioner has proposed the use of L-carnitine in dairy-based formulas as well as soy-based formulas. According to a scientific panel advising the European Food Safety authority, L-carnitine is found naturally in dairy-based formulas and is not considered a necessary supplement for this type of formula (EFSA, 2003a). Moreover, the European Commission's Scientific Committee on Food affirmed that the addition of L-carnitine to cows' milk-based formula or to follow-on formula is unnecessary because cow's milk is naturally rich in carnitine (around 5 mg/100 kcal). The Committee also concluded that L-carnitine supply from appropriate complementary food and from endogeneous synthesis should be sufficient in older infants. Only the liver butyrobetaine hydroxylase, the last enzyme in carnitine biosynthesis, shows age-dependent low activity in young infants. The activity of the kidney enzyme and the other three biosynthetic enzymes in the liver and other tissues are not age-dependent (EFSA, 2003b). The petitioner contends, however, that additional L-carnitine should be added to dairy-based formulas because the carnitine in dairy-based infant formula has reduced bioavailability and because cow's milk must be diluted prior to its use in infant formula. While the petitioner agrees that cow's milk initially contains adequate levels of L-carnitine, they report that dilution is necessary to attain a more appropriate protein level for infants (IFC, 2011). This dilution step has been verified (USDA, 2012); however the impact on L-carnitine levels in milk-based infant formulas could not be confirmed.

L-carnitine is used as a treatment for nervous system degenerative diseases, brain/heart ischemia, chronic fatigue syndrome, Alzheimer's disease, and AIDS. Carnitine supplementation has also been shown to improve erythrocyte function in hemodialysis patients (Lango et al., 2001). The effectiveness of L-carnitine for some of these conditions is unclear and requires further research (Linus Pauling Institute, 2007).

L-carnitine is added to some pet foods, such as Iams brand conventional dog food (P&G Pet Care, 2012) and Organix Weight Management dog food (Castor and Pollux, 2012), as a dietary supplement for weight control purposes. Although its effectiveness as a weight loss therapy has not been scientifically verified in humans (EFSA, 2003a), there is some indication that L-carnitine may be useful in treating obese pets (Center et al., 2008).

Approved Legal Uses of the Substance:

Food Additive/Dietary Supplement

L-carnitine (synthetic or nonsynthetic) is not currently included on the National List of Allowed and Prohibited Substances (hereafter referred to as the National List) of nonagricultural (nonorganic) 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).

FDA regulations on the nutrient requirements of infant formula (21 CFR 107.100(a)) do not require the addition of L-carnitine. L-carnitine has not been affirmed as GRAS by the FDA as a nutrient and/or dietary supplement (21 CFR 582; FDA, 2012). However, L-carnitine may have been self-affirmed as GRAS. See Evaluation Question #4 for more information on the GRAS status of L-carnitine.

L-carnitine 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 it regulates 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 FDA is responsible for taking action regarding an unsafe product after it reaches the market and making sure the supplement's label is accurate and not misleading (FDA, 2005).

Pet foods do not need to be approved by the FDA before they enter the market; however, additives including minerals, vitamins or other nutrients, flavorings, preservatives, or processing aids must be generally recognized as safe (GRAS) for their intended use (21 CFR 582 and 584) or have approval as food additives in animal feed (21 CFR 570, 571 and 573). Although L-carnitine does not appear in any of this legislation, the FDA's Center for Veterinary Medicine (CVM) has reviewed safety information for L-carnitine and allowed it to be used in dog food, even though it is officially an "unapproved food additive" (Dzanis, 1999). While not a regulatory body, the Association of American Feed Control Officials (AAFCO) has approved L-carnitine for use in swine feed, in chicken and turkey feed, in fish feed, in ruminant milk replacer, and in pet food (AAFCO, 2012; Zoran, 2002).

Therapeutic Uses

Levocarnitine (L-carnitine) injection (200 mg/mL) is approved by the FDA for therapeutic use in patients with carnitine deficiency (FDA, 2001). L-carnitine is often administered intravenously to hemodialysis patients following a dialysis treatment in order to replenish the free carnitine removed from blood during the procedure and to combat malnutrition common in these patients (Flanagan et al., 2010). In March 2007, Carnitor® SF oral solution was approved by the FDA to treat primary systemic carnitine deficiency and for acute and chronic treatment of patients with genetic metabolic disorder that results in a secondary carnitine deficiency (FDA, 2007; MNT, 2007). FDA has listed a maximum recommended therapeutic dose of 16.7 mg/kg-bw/day for carnitine and 49.5 mg/kg-bw/day for levocarnitine (equivalent to roughly 1 and 3 g per day, based on an average 60-kg person as used by FDA) (FDA, 2009). While no verification was provided on the website, based on the differing structures listed and the CASRNs associated with each structure, FDA has likely provided a recommended maximum dose for each of two forms, L-carnitine, CASRN 541-15-1 ("levocarnitine"), and D,L-carnitine, CASRN 461-06-3 ("carnitine").

Action of the Substance:

One of the main functions of L-carnitine is to facilitate the entry of long-chain fatty acids, necessary for energy generation, into mitochondria. Long-chain fatty acids cannot enter mitochondria without being translocated as an ester of carnitine. L-carnitine also facilitates the removal of short-chain and medium-chain fatty acids that may build up in the mitochondria as the result of metabolism (Rebouche, 1992). Primary carnitine deficiency (caused by a rare, recessive a genetic disorder) is manifested by symptoms of cardiomyopathy (weakened and enlarged heart), skeletal-muscle weakness, and hypoglycemia (low blood sugar). Secondary carnitine deficiencies (caused by other genetic or metabolic disorders) may result from certain disorders (such as chronic renal failure) and result in high carnitine excretion in the urine (Flanagan et al., 2010).

L-carnitine may protect against ischemic heart injury, possibly by scavenging free radicals or by preventing their formation in cardiac muscle. L-carnitine may also protect other cells from oxidative damage by inhibiting the propagation of free radicals and helping to repair oxidized membrane phospholipids (Rebouche, 1992). L-carnitine concentration in the heart is more than three times that in striated muscles, four times that in the liver, and eight times that in the kidney, emphasizing the particular importance of carnitine availability to the heart. L-carnitine is synthesized primarily in the kidneys and liver; the heart does not synthesize carnitine, but extracts it from plasma (Lango et al., 2001). Please see Evaluation Question #10 for more information on the potential health benefits from the therapeutic or supplemental use of L-carnitine.

For unknown reasons, the bioavailability of L-carnitine in supplements is not as high as its bioavailability from natural sources. The bioavailability of oral carnitine supplements is only about 14–18% of the administered dose, indicating that much of the substance is not absorbed and used by the body (Flanagan et al., 2010). In contrast, the bioavailability of L-carnitine from food in omnivores is about 54–72% (Linus Pauling Institute, 2007).

Combinations of the Substance:

L-carnitine is petitioned for addition to the National List (at 7 CFR 205.605(b)) for use as a synthetic additive 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).

L-carnitine may also be combined with other nutrients and vitamins when used as a dietary supplement. For example, Lonza Group, Ltd. produces L-carnitine L-tartrate (trade name Carnipure™), which consists of 68% L-carnitine and 32% L-tartaric acid (Held, 2004). Since 2003, tartaric acid has been included on the National List as a nonagricultural (nonorganic) substance allowed as an ingredient in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))" (7 CFR 205.605). This material is listed both as a nonsynthetic allowed substance (7 CFR 205.605(a)) if made from grape wine (i.e., L(+) tartaric acid) and a synthetic allowed substance (7 CFR 205.605 (b)) if made from malic acid (i.e., a synthetic form of L(+) tartaric acid) (NOSB, 2011). In December 2011, the NOSB issued a formal recommendation that the allowance for synthetic tartaric acid on section 205.605(b) be allowed to sunset (expire) on November 3, 2013. This recommendation has not yet been implemented by the National Organic Program (NOSB, 2011).

Status

Historic Use:

L-carnitine was first isolated from muscle tissue in 1905; its structure was determined in 1927 (Held, 2007). It has been promoted as a beneficial nutritional supplement and therapeutic agent since the 1960s (Flanagan et al., 2010). Carnitine was first linked to treatment of circulatory disorders in 1973 when

researchers found that patients with lipid cardiomyopathy and reduced fatty acid oxidation were deficient in L-carnitine (Lango et al., 2001).

According to the petitioners, L-carnitine has been added to soy-based infant formula since 1986 and milk-based formula since the 1990s (IFC, 2011). The history of the legal use of L-carnitine in organic handling/processing has revolved around uncertainty over the nutritional status of L-carnitine because it is neither a vitamin nor a mineral. Originally, the National Organic Program (NOP) interpreted that under 21 CFR 104.20(f), which states that "nutrient(s) may be added to foods as permitted or required by applicable regulations established elsewhere in this chapter," L-carnitine 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 L-carnitine. See "OFPA, USDA Final Rule" for more information.

OFPA, USDA Final Rule:

L-carnitine (synthetic or nonsynthetic) is not currently listed under 7 CFR 205.605 as a nonagricultural (nonorganic) substance allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients or food group(s))."

The NOP final rule limits "vitamins and minerals" allowed for use in organic products to those in the FDA Nutritional Quality Guidelines for Food (21 CFR § 104.20(d)(3)), which does not include L-carnitine. However, due to a previous misinterpretation of the regulations, some organic infant formulas do contain synthetic L-carnitine and other nutrient additives. Brands with added L-carnitine include dairy-based Similac Organic (IFC, 2011), soy-based Earth's Best Organic Soy Infant formula (Earth's Best Organic, 2012), and soy-based Baby's Only Organic Soy Formula (Nature's One, 2012). However, it appears not all infant formulas are supplemented with L-carnitine, including a dairy-based organic formula from Vermont Organics (IFC, 2011), Baby's Only Organic® Dairy formula with DHA & ARA (Nature's One, 2012), and Earth's Best Organic Infant Formula with DHA & ARA (Earth's Best Organic, 2012).

To clarify the regulatory applicability for nutrient additives, the NOP published a proposed rule in January 2012 (77 FR 1980) that would clarify the required nutrients under the NOP regulations. Nutrients which are not required, including L-carnitine, would no longer be allowed unless the NOSB issues recommendations to add them to the National List and such recommendations are codified through rulemaking. If promulgated as a final rule, this amendment would clarify that L-carnitine is not one of the required nutrients allowed in organic products (USDA, 2012).

International:

L-carnitine is not included on the Canadian General Standards Board's (CGSB's) Permitted Substances List for Processing. However, the CGSB's General Principles and Management Standards (CAN/CGSB-32.310-2006), Section 8.3.4, provides the following information related to the use of food additives and processing aids (CGSB, 2009).

> *Food additives and processing aids shall only be used to maintain:*
> *a. nutritional value;*
> *b. food quality or stability;*
> *c. composition, consistency and appearance, provided that their use does not mislead the consumer concerning the nature, substance and quality of the food; and*
> > *i. there is no possibility of producing a similar product without the use of additives or processing aids;*
> > *ii. they are not included in amounts greater than the minimum required to achieve the function for which they are permitted.*

Based on this information, it is assumed that organic soy-based infant formula could legally be fortified with L-carnitine for nutritional purposes. However, L-carnitine is not legally required in infant formulas per Section B.25.054 of Health Canada's Food and Drug Regulations.

Section 3.5 of the Codex Standards for organically-raised foods includes the following information related to essential fatty and amino acids in food products (Codex Alimentarius Commission, 2010).

> *Minerals (including trace elements), vitamins, essential fatty and amino acids, and other nitrogen compounds [are] only approved in so far as their use is legally required in the food products in which they are incorporated.*

The Codex Alimentarius Commission's "Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children" requires a minimum content of 1.2 mg/100 kcal of L-carnitine in infant formula (Codex Alimentarius Commission, 2011).

The European Commission Regulation EC No. 889/2008, Article 27, provides information related to the use of certain products and substances in the processing of food (European Commission, 2008).

> *For the purpose of Article 19(2)(b) of Regulation (EC) No 834/2007, only the following substances can be used in the processing of organic food, with the exception of wine: (a) substances listed in Annex VIII to this Regulation;… (f) minerals (trace elements included), vitamins, amino acids, and micronutrients, only authorised as far their use is legally required in the foodstuffs in which they are incorporated.*

L-carnitine does not appear on the list of products in Annex VIII of EC No. 889/2008. However, the Commission Directive 91/321/EEC from May 14, 1991, on infant formula and follow-on formula states that soy protein infant formula must contain a minimum of 7.5 µmoles of L-carnitine/100 kcal of formula; there is no maximum amount recommended. Thus, it appears that L-carnitine is required in organic infant formula, but other foods do not have legal requirements for the inclusion of L-carnitine. L-carnitine and L-carnitine hydrochloride are also permitted in Europe for use in conventional foods for infants and young children including processed cereal-based foods and baby foods (EFSA, 2003a).

The International Federation of Organic Agriculture Movements (IFOAM) does not list L-carnitine within its "Norms for Organic Production and Processing" (IFOAM, 2006) but, relative to organic food processing, provides the following information (IFOAM, 2010).

> *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 in the market to which the particular batch of product is destined.*

The Japan Agricultural Standard (JAS) for Organic Processed Foods (JMAFF, 2006) does not mention the use of L-carnitine in organic foods. General principles state that organic processed food should be made "avoiding the use of chemically synthesized food additives and chemical agents" (JMAFF, 2006). No other relevant information is provided.

Evaluation Questions for Substances to be used in Organic Handling

<u>Evaluation Question #1:</u> 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)).

L-carnitine can be manufactured in nonsynthetic and synthetic forms. There are several chemical manufacturing processes for L-carnitine. L-carnitine is usually synthesized using epichlorhydrine or trimethylamine, and racemate separation by fractionated crystallization or other methods (Meyer and Robins, 2005). L-carnitine can also be obtained from industrially-produced D-mannitol (Fiorini et al., 1983).

Sigma-Aldrich produces a synthetic form of L-carnitine hydrochloride (Sigma Aldrich, 2012). L-carnitine can also be manufactured through enantioselective synthesis from glycerol (HSDB, 2008); it is assumed that this is a synthetic, chemical process. The acetyl ester of L-carnitine, acetyl-L-carnitine, is produced from acetylation of L-carnitine (Technical Resources International, 2004).

L-carnitine can also be produced using commercially available biosynthetic or fermentative methods; however, it is not always clear if the L-carnitine produced would be considered nonsynthetic. Using biosynthetic methods, L-carnitine is obtained via microorganisms (e.g., *Escherichia coli, Proteus mirabilis*) cultivated in a bioreactor with crotonobetaine, crotonobetaine salts, or its derivatives (IFC, 2011; Büchner and Paradies, 2011). For this method, however, the required precursors may be chemically synthesized (Naidu et al., 2000) so the final product could be considered synthetic. For example, crotonobetaine is often used as a precursor, but this substance is most easily obtained from racemic DL-carnitine, which is synthetic.

Another microbiological process involves depleting a cultured solution of pure L-carnitine by electrodialysis followed by recrystallization of the L-carnitine. No D-carnitine is produced in this method and thus separation of the enantiomers is not necessary (Büchner and Paradies, 2011). It is apparent that some biosynthetic production methods utilize biotechnology (requiring genetically-modified bacteria; Meyer and Robins, 2005), which is not allowed in organic processing and handling (7 CFR 205.105(e)). It is unclear which biosynthetic producers of L-carnitine use genetically-modified microorganisms, but it appears biosynthetic methods that do not use genetically-modified organisms are available (Held, 2007). Fermentative processes do not use L-carnitine precursor substrates (e.g., crotonobetaine), but involve the cultivation of bacterial or fungal cells incubated with sugar, oils, starch, molasses, or other media. Several Japanese companies, including Nippon Pet Food, Yakult Honsha, and Takeda Chemical, claim to utilize fermentative methods to produce L-carnitine (Naidu et al., 2000). It appears that while these processes would produce nonsynthetic L-carnitine, the companies using these fermentative methods are not the main suppliers of L-carnitine in the United States. Companies that use biosynthetic methods, including Lonza Group, Ltd., are the predominant manufacturers for the U.S. market (IFC, 2011).

Although L-carnitine can also be extracted from natural sources like red meat, this nonsynthetic form of production is not commercially economically viable. Furthermore, if production is not adequately controlled, animal-derived products may have the potential to contain bacteria, viruses, and other contaminants (Meyer and Robins, 2005).

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).

L-carnitine can be manufactured in synthetic and nonsynthetic forms. As discussed under Evaluation Question #1, L-carnitine can be produced from chemical synthesis, but may also be produced from microbial, enzymatic, or fermentative processes. Based on information provided by Held (2007), it is possible to produce L-carnitine nonsynthetically through biosynthesis without using genetically-modified organisms; however, in some cases, biotechnology is used, which would not be allowed in organic processing and handling.

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

L-carnitine can be obtained from the diet. It is present in a variety of foods, including beef steak and ground beef (80–81 mg/3 oz.), pork (24 mg/3 oz.), milk (8 mg/8 fl. oz.), chicken breast (3 mg/3 oz.), avocado (2 mg/1 medium fruit), and asparagus (0.2 mg/0.5 cups) (Linus Pauling Institute, 2007).

As described under Evaluation Question #2, bacteria may also produce L-carnitine through fermentation—a nonsynthetic process (Held, 2007). Biosynthetic processes like those described by Lonza Group, Ltd. would also be considered nonsynthetic (Held, 2007; Meyer and Robins, 2005).

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?

L-carnitine has not been categorized as GRAS by the FDA as a nutrient and/or dietary supplement (21 CFR 582; FDA, 2012). In November of 2010, Northeast Pharmaceutical Group (2010) petitioned the FDA to consider levocarnitine (L-carnitine) as GRAS for use as a food ingredient. The company expressed the intention of using it in chewable tablets and capsules, milk powder, formula, sports drinks, and fruit or fruit-flavored beverages. The company based its GRAS identification on "published scientific data, including pharmacokinetic studies, toxicity studies, and studies in humans that suggested the safety of L-carnitine." However, for an unknown reason, the company requested on March 8, 2011, that FDA cease to evaluate the GRAS notice, and FDA complied (FDA, 2011). The European Food Safety Authority claimed in a report that L-carnitine-L-tartrate (produced by Lonza Group, Ltd.) was "self-determined" as GRAS and has been sold under the GRAS status since 1993, but this information could not be substantiated (EFSA, 2003a). An internet news source also reported that "an external scientific panel" determined that Lonza Group, Ltd.'s products, crystalline L-carnitine, and L-carnitine-L-tartrate, were considered GRAS for use in food (Nutra Ingredients, 2002), but again this could not be confirmed by another source. No further information about the GRAS status of L-carnitine was identified.

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)).

There are no data indicating that L-carnitine has preservative properties. Its main function is as a dietary supplement or therapeutic agent.

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)).

L-carnitine is not used to recreate or improve flavors, colors, or textures of food. While its purpose is to increase the nutritional value of foods or provide supplemental nutrition, it is not intended to replace nutrients lost during processing.

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

L-carnitine is used to improve the nutritional quality of food and pet food or as a dietary supplement to provide additional L-carnitine to adults with insufficient dietary intake or endogenous production. In general, healthy individuals (other than infants) can synthesize sufficient amounts of L-carnitine endogenously; thus, supplementation is usually intended for those with primary and secondary L-carnitine deficiencies (Linus Pauling Institute, 2007). When added to infant formula, L-carnitine is intended to improve the nutritional content of the formula, in particular for soy-based formulas that are naturally low in L-carnitine. Infants cannot endogenously synthesize adequate amounts of L-carnitine and must obtain much of the required L-carnitine from their diet (British Pediatric Association, 1996).

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 information regarding residues of heavy metals or contaminants in L-carnitine was identified. It should be noted, however, that makers of dietary supplements can voluntarily apply for verification by U.S. Pharmacopeia (USP), which has strict requirements for purity, potency, and quality of dietary

supplements (USP, 2012). A dietary supplement marked with a "USP Verified" label reportedly "does not contain harmful levels of specified contaminant" including heavy metals (e.g., lead and mercury), pesticides, bacteria, molds, toxins, or other contaminants (USP, 2012). USP dietary supplements cannot contain more than 10 µg of lead, 15 µg of arsenic or total mercury, 2 µg of methyl mercury (as Hg), or 5 µg of cadmium (USP, 2010), suggesting that any L-carnitine supplement that is USP verified would not contain metals at levels above these limits.

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)).

The manufacture of L-carnitine through chemical synthesis and biosynthetic processes produce waste products that can enter the environment. According to Meyer and Robins (2005), the biosynthetic processes like those used by Lonza Group, Ltd. produce less waste than chemical synthesis. It was estimated that Lonza's biosynthetic process generates around 0.5 tons of waste per ton of L-carnitine produced, while chemical synthesis generates about 4.5 tons of waste per ton of L-carnitine produced. Furthermore, it was estimated that biosynthesis yields approximately 40 m^3 of wastewater per ton of L-carnitine produced, while chemical synthesis yields around 220 m^3 of wastewater per ton of L-carnitine produced (Meyer and Robins, 2005).

Workers in L-carnitine production may be exposed to chemical intermediates and final products with some risk of health effects either during normal manufacturing processes or accidents. For example, accidental fire of L-carnitine hydrochloride can cause hazardous decomposition products including carbon oxides, nitrogen oxides (NOx), and hydrogen chloride gas (Sigma Aldrich, 2012). Hydrogen chloride is irritating and corrosive to the eyes, skin, and mucous membranes, and exposure to high concentrations can cause pulmonary edema, burns of the skin and mucous membranes, and blindness (if the solution comes in contact with eyes) (OSHA, undated).

No other information on the environmental fate or ecological effects of L-carnitine was found.

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)).

L-carnitine deficiency is well characterized in the literature, and it may be caused by a number of genetic and metabolic disorders. For example, primary carnitine deficiency syndrome occurs in children aged 1 to 7 years old; it is the result of a rare autosomal recessive disorder of fatty acid oxidation. Secondary carnitine deficiency occurs for a variety of reasons, including metabolic disorders or hemodialysis, and is characterized by increased carnitine excretion in the urine (Flanagan et al., 2010). In these cases, L-carnitine supplementation is recommended to improve health.

Due to the low content of L-carnitine in soy-based infant formulas and an apparent inability of infants (particularly premature infants) to synthesize adequate amounts of L-carnitine endogenously, L-carnitine is often recommended as a nutritional supplement in these types of infant formulas (British Pediatric Association, 1996). L-carnitine is found naturally in dairy-based formulas. Advisory studies published by the European Food Safety Authority state that L-carnitine supplementation is not necessary for these formulas (EFSA, 2003a; IFC, 2011). However, as discussed under "Specific Uses of the Substance," the petitioner contends that L-carnitine supplementation of dairy-based formulas is appropriate due to dilution and bioavailability issues. i

In one study, the benefits of L-carnitine supplementation were not apparent for some common challenges in preterm infants. O'Donnell et al. (2002) performed a prospective, blinded trial on 44 preterm infants in which L-carnitine was administered at doses of 30 mg/kg-day from ≤32–34 weeks of gestational age. Despite earlier reports to the contrary, O'Donnell et al. (2002) found that supplemental L-carnitine did not reduce apnea of prematurity (short episodes of stopped breathing), the number of days in which a

ventilator or nasal continuous positive airway pressure was needed, or the need for supplemental oxygen. Although the benefits are somewhat contested, the European Food Safety Authority has reviewed available data and determined that common forms of L-carnitine, including L-carnitine-L-tartrate, are "not of concern from the safety point of view as a source of L-carnitine for use in foods for particular nutritional uses [e.g., in infant formula], provided the Acceptable Daily Intake for tartaric acid from all sources in the diet [0–30 mg/kg-bw] is not regularly exceeded" (EFSA, 2003a).

L-carnitine may be used as a therapeutic agent in several of its forms. One of its common therapeutic uses is to treat heart conditions such as coronary heart disease, chronic heart failure, and peripheral vascular disease. In addition, L-carnitine can help reduce myocardial injury in patients with heart ischemia (Flanagan et al., 2010; Lango et al., 2001). L-carnitine is also being investigated as a treatment for numerous other conditions. Data from a number of studies suggest that L-carnitine supplementation may be useful in treating men with infertility and/or sperm motility disorders (Linus Pauling Institute, 2007). Other studies have indicated that acetyl-L-carnitine, the acetyl ester of L-carnitine, is a promising treatment for neurodegenerative diseases such as hepatic encephalopathy, dementia, and Alzheimer's disease (Flanagan et al., 2010). Youle et al. (2007) found that administration of acetyl-L-carnitine significantly reduced weekly mean pain ratings in HIV-infected patients and improved their symptoms as a whole compared with a placebo. These authors also reported that this supplement, at doses of 500 mg twice a day, was well tolerated and "generally safe." No significant side effects were reported (Youle et al., 2007). Some research also suggests that L-carnitine supplementation may be used to treat obesity as well as decreased immune function in diabetics, but additional research to support these claims is required (Flanagan et al., 2010).

In general, therapeutic doses of L-carnitine are not toxic; adverse effects are infrequent and not severe. High doses (~4,000–6000 mg/kg-day) can cause nausea, vomiting, abdominal cramping, and diarrhea (EFSA, 2003a). Doses of greater than 3,000 mg/kg-day can cause unpleasant, fishy body odor, but these effects go away when the dose is reduced (British Pediatric Association, 1996; Linus Pauling Institute, 2007). The D-isomer of carnitine may compete with L-carnitine for absorption and transport and has been associated with deleterious effects; thus, D-carnitine and D,L-carnitine mixtures should be avoided (Linus Pauling Institute, 2007).

L-carnitine supplement makers often claim that L-carnitine supplementation use is beneficial to athletic performance; however, data currently do not support this claim. According to a review by the Scientific Committee on Food, "available information, including controlled studies in humans during exercise, did not support commercial claims that carnitine supplementation helps weight loss and improves physical performance" (EFSA, 2003a).

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

No organic agricultural products have been identified that could serve as alternatives to L-carnitine for use in dietary supplements, therapeutic agents, infant formulas, and foods. Specifically, no organic alternative for soy-based infant formula capable of supplying sufficient amounts of L-carnitine to infants was identified.

Diet is an important source of L-carnitine. As discussed under Evaluation Question #3, L-carnitine is present in a variety of foods, including beef steak and ground beef (80–81 mg/3 oz.), pork (24 mg/3 oz.), milk (8 mg/8 fl. oz.), chicken breast (3 mg/3 oz.), avocado (2 mg/1 medium fruit), and asparagus (0.2 mg/0.5 cups) (Linus Pauling Institute, 2007). These products all are available from organic producers, however these products would not be suitable for the diets of infants and sufficient levels of L-carnitine would not be obtained.

Although vegetarians do not eat meat, which is one of the best dietary sources of L-carnitine, research indicates that vegetarians can sustain sufficient levels of L-carnitine through diet and from endogenous production, making L-carnitine supplementation unnecessary (Linus Pauling Institute, 2007). This

suggests that endogenous production of L-carnitine plus dietary intake of L-carnitine from food provide adequate levels for most healthy adults.

References

AAFCO, 2012. Official Publication, Association of American Feed Control Officials, Inc. Oxford, IN.

British Pediatric Association. 1996. Annotation: L-carnitine. Archives of Disease in Childhood 74: 475-478. Retrieved February 15, 2012 from http://adc.bmj.com/content/74/6/475.full.pdf

Büchner T, and Paradies, G. 2011. Methods for the production of L-carnitine. U.S. Patent 2011/0118503 A1. Retrieved February 15, 2012 from http://www.google.com/patents?id=JYfiAQAAEBAJ&pg=PA2&dq=l-carnitine&hl=en&sa=X&ei=6tg7T-PFFc3ptQa416n5Bg&ved=0CE8Q6AEwCQ#v=onepage&q=l-carnitine&f=false

Castor & Pollux. 2012. Organix Weight Management adult dog food. Retrieved April 18, 2012 from http://www.castorpolluxpet.com/product/organix-weight-management-adult-dog-food

Center, S.A., Harte, J., Watrous, D., Reynolds, A., Watson, T.D.G., Markwell, P.J., Millington, D.S., Wood, P.A., Yeager, A.E., Erb, H.N. 2008. The clinical and metabolic effects of rapid weight loss in obese pet cats and the influence of supplemental oral L-carnitine. Journal of Veterinary Medicine 14(6):598-608. [abstract] Retrieved April 18, 2012 from http://onlinelibrary.wiley.com/doi/10.1111/j.1939-1676.2000.tb02283.x/abstract

ChemIDplus Lite. 2012. L-Carnitine. Retrieved February 14, 2012 from http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp

CGSB (Canadian General Standards Board). 2009. General Principles and Management Standards: CAN/CGSB-32.310-2006. Amended June 2011. Retrieved February 17, 2012 from http://www.tpsgc-pwgsc.gc.ca/ongc-cgsb/programme-program/norms-standards/internet/bio-org/documents/032-0310-2008-eng.pdf

Codex Alimentarius Commission. 2011. Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children. CAC/GL 10 – 1979. Retrieved February 15, 2012 from http://www.codexalimentarius.net/download/standards/288/CXS_072e.pdf

Codex Alimentarius Commission. 2010. Guidelines for the Production, Processing, Labelling, and Marketing of Organically Produced Foods. Retrieved February 20, 2012 from http://www.codexalimentarius.net/download/standards/360/cxg_032e.pdf

Dzanis, D. 1999. Interpreting pet food labels – Part 2: Special food uses. FDA Veterinarian Newsletter January/February 1999. Retrieved April 18, 2012 from http://www.fda.gov/animalveterinary/newsevents/fdaveterinariannewsletter/ucm090102.htm

Earth's Best Organic. 2012. Our products. Retrieved February 15, 2012 from http://www.earthsbest.com/

European Commission. Commission Regulation (EC) No 889/2008. Retrieved March 15, 2012 from http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:250:0001:0084:EN:PDF

European Food Safety Authority (EFSA). 2003a. Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to L-Carnitine-L-tartrate for use in foods for particular nutritional uses. Retrieved February 24, 2012 from http://www.efsa.europa.eu/en/efsajournal/doc/19.pdf

European Food Safety Authority (EFSA). 2003b. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. Retrieved April 30, 2012 from http://ec.europa.eu/food/fs/sc/scf/out199_en.pdf

FDA (U.S. Food and Drug Administration). 2012. Food additive status list. Retrieved February 17, 2012 from http://www.fda.gov/Food/FoodIngredientsPackaging/FoodAdditives/FoodAdditiveListings/ucm091048.htm

FDA (U.S. Food and Drug Administration). 2011. Agency response letter GRAS Notice No. GRN 000362 CFSAN/Office of Food Additive Safety. Retrieved February 17, 2012 from http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm250925.htm

FDA (U.S. Food and Drug Administration). 2009. Maximum recommended therapeutic dose (MRTD) database. Retrieved February 17, 2012 from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm092199.htm

FDA (US Food and Drug Administration). 2007. March 2007: Additions and deletions to the drug product list. Retrieved March 15, 2012 from http://www.fda.gov/Drugs/InformationOnDrugs/ucm089671.htm

FDA (US Food and Drug Administration). 2005. Dietary supplements. Retrieved February 17, 2011 from http://www.fda.gov/food/dietarysupplements/default.htm

FDA (US Food and Drug Administration). 2001. Approvals March 2001. Retrieved March 15, 2012 from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm063392.htm

Fiorini, M.; Valentini, C. 1983. Method for preparation of L-carnitine. U.S. Patent 413142. Retrieved February 15, 2012 from http://www.google.com/patents?id=fdw3AAAAEBAJ&pg=PA6&dq=l-carnitine&hl=en&sa=X&ei=6tg7T-PFFc3ptQa416n5Bg&ved=0CEwQ6AEwCA#v=onepage&q=l-carnitine&f=false

Flanagan, J.L.; Simmons, P.A.; Vehige, J.; Willcox, M.D.P.; Garrett, Q. 2010. Role of carnitine in disease. Nutrition & Metabolism 7:30. Retrieved February 20, 2012 from http://www.nutritionandmetabolism.com/content/7/1/30

Held, U.S. 2007. L-Carnipure in human nutrition. Chimia 61: 8-10. Retrieved February 15, 2012 from http://www.lonza.com/about-lonza/media-center/~/media/EF6A76C20B824B819285D0DBABDBFCB7.ashx

Held, U.S. 2004. L-Carnitine – The natural choice for functional foods. Retrieved February 15, 2012 from http://www.lonza.com/about-lonza/media-center/~/media/C8ABFF8879714C3A89C308A5397B62D7.ashx

HSDB (Hazardous Substances Databank). 2008. L-Carnitine; last updated 8-26-2008. Retrieved February 14, 2012 from http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

IFC (International Formula Council). 2011. Petition for the inclusion of L-carnitine on the National List at §205.605(b) as a non-agricultural (non-organic) substance allowed in or on processed products labeled as "organic" or "made from organic (specified ingredients)." November 11, 2011.

IFOAM (International Federation of Organic Agriculture Movements). 2010. The IFOAM Standard for

Organic Production and Processing; Version 2010 – Draft version 0.1. Compilation of comments and responses from the IFOAM Standard Committee. Retrieved February 23, 2012 from http://www.ifoam.org/about_ifoam/standards/norms/IS_V0.1.withcommentsandresponses_final20110819.pdf

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

JMAFF (Japanese Ministry of Agriculture, Forestry and Fisheries). 2006. Japanese Agricultural Standard for Organic Processed Foods. Notification No. 1606. Retrieved February 15, 2012 from http://www.maff.go.jp/e/jas/specific/pdf/1416_2006.pdf

Lango, R., Smolenski, R.T., Narkiewicz, M., Suchorzewska, J., Lysiak-Szydlowska, W. 2001. Influence of L-carnitine and its derivatives on myocardial metabolism and function in ischemic heart disease and during cardiopulmonary bypass. Cardiovascular Research 51:21-29. Retrieved February 14, 2012 from http://cardiovascres.oxfordjournals.org/content/51/1/21.full.pdf+html

Linus Pauling Institute. 2007. L-Carnitine. Micronutrient Information Center, Oregon State University. Retrieved February 15, 2012 from http://lpi.oregonstate.edu/infocenter/othernuts/carnitine/

Meyer, H.-P., Robins, K.T. 2005. Large scale bioprocess for the production of optically pure L-carnitine. Monatshefte fur Chemie 136:1269-1277. Retrieved February 20, 2012 from http://www.lonza.com/about-lonza/media-center/~/media/A6BCD2AC6A3349658D66A37B5FF18F20.ashx

Medical News Today (MNT). 2007. FDA approves Carnitor(R) SF (Levocarnitine) sugar-free oral solution for patients with carnitine deficiency. June 23, 2007. Retrieved February 17, 2012 from http://www.medicalnewstoday.com/releases/75033.php

Naidu, G.S.N.; Lee, I.Y.; Lee, E.G.; Kang, G.H.; Park, Y.H. 2000. Microbial and enzymatic production of L-carnitine. Bioprocess Engineering 23: 627-635.

NOSB (National Organic Standards Board) Handling Committee. 2011. Sunset 2013 Proposed Recommendation; Tartaric acid on §205.605(a) and §205.605(b). December 2, 2011. Retrieved March 8, 2012, from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5097107

Nature's One. 2012. Organic pediatric nutrition. Retrieved February 15, 2012 from http://www.naturesone.com/

Northeast Pharmaceutical Group. 2010. GRAS notice for levocarnitine. Retrieved February 17, 2012 from http://www.accessdata.fda.gov/scripts/fcn/gras_notices/GRN000362.pdf

Nutra Ingredients. 2002. Lonza announces GRAS status for L-carnitine products. Retrieved March 15, 2012 from http://www.nutraingredients.com/Consumer-Trends/Lonza-announces-GRAS-status-for-L-carnitine-products

O'Donnell, J., Finer, N.N., Rich, W., Barshop, B., Barrington, K.J. 2002. Role of L-carnitine in apnea of prematurity: A randomized, controlled trial. Pediatrics 109(4): 622-626. Retrieved February 15, 2012 from http://pediatrics.aappublications.org/content/109/4/622.abstract [abstract].

OSHA (Occupational Health and Safety Administration). Undated. Occupational safety and health guideline for hydrogen chloride. Retrieved February 20, 2012 from http://www.osha.gov/SLTC/healthguidelines/hydrogenchloride/recognition.html

P&G Pet Care. 2012. Iams® ProActive Health. Retrieved April 18, 2012 from http://www.iams.com/dog-food/iams-proactive-health-adult-active-maturity-small-toy-breed

Rebouche, C.J. 1992. Carnitine function and requirements during the life cycle. The FASEB Journal 6:3379-3386. Retrieved February 14, 2012 from http://www.fasebj.org/content/6/15/3379.full.pdf

Sigma Aldrich. 2012. L-carnitine hydrochloride. Retrieved February 15, 2012 from http://www.sigmaaldrich.com/catalog/ProductDetail.do?D7=0&N5=SEARCH_CONCAT_PNO%7CBRAND_KEY&N4=C0283%7CSIGMA&N25=0&QS=ON&F=SPEC

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 16, 2012 from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5096390

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 February 29, 2011 from http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5084068&acct=nosb

USDA. 2012. Chapter 4: Infant Formula and Feeding. Retrieved April 30, 2012 from http://wicworks.nal.usda.gov/infants/infant-feeding-guide

USP (U.S. Pharmacopeia). 2012. The USP dietary supplement verification program. Retrieved March 15, 2012 from http://www.usp.org/USPVerified/dietarySupplements/

USP (U.S. Pharmacopeia). 2010. Limits of elemental contaminants. Pharmacopeial Forum 36(1):1-9. Retrieved March 15, 2012 from http://www.usp.org/pdf/EN/hottopics/2232ElementalContaminantsDietarySupplements.pdf

Technical Resources International. 2004. Acetyl-L-carnitine/α-lipoic acid supplements. Retrieved February 24, 2012 from http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/carnliposupp.pdf

Vitamin Shoppe. 2012. Carnipure L-carnitine. Retrieved February 15, 2012 from http://www.vitaminshoppe.com/store/en/browse/sku_detail.jsp?id=VS-1698#tab2

Youle, M., Osio, M., on behalf of ALCAR study group. 2007. A double-blind, parallel-group, placebo-controlled, multicentre study of acetyl L-carnitine in the symptomatic treatment of antiretroviral toxic neuropathy in patients with HIV-1 infection. HIV Medicine 8(4):241-250. Retrieved February 15, 2012 from http://onlinelibrary.wiley.com/doi/10.1111/j.1468-1293.2007.00467.x/full

Zoran, D.L. 2002. The carnivore connection to nutrition in cats. JAVMA 221 (11):1559-1567. Retrieved April 18, 2012 from http://www.purebredsplus.org/links/zorans_article.pdf