L-Methionine
Handling/Processing

Identification of Petitioned Substance

Chemical Names:
L-methionine
L-2-amino-4-(methylthio)butyric acid
(s)-(+)-2-amino-4-(methylthio)butyric acid
(s)-2-amino-4-(methylthio)butanoic acid
2-amino-4-(methylthio)butanoic acid
2-amino-4-(methylthio)-butyric acid
2-amino-4-methylthiobutanoic acid

Other Names:
Methionine

Trade Names:
L-Methionine USP/FCC
Cymethion
Acimethin

CAS Number:
63-68-3

Other Codes:
200-562-9 (EINECS number)
PD0457000 (RTECS number

Characterization of Petitioned Substance

<u>**Composition of the Substance**</u>:

Amino acids have an amino group (NH_2) adjacent to a carboxyl (COOH) group on a carbon. Methionine, with an empirical formula of $C_5H_{11}NO_2S$, is a sulfur-containing essential amino acid. The molecular structures of the two enantiomers of methionine are shown in Figure 1 and Figure 2. In these figures, differences in the three-dimensional structure of the enantiomers are indicated by how the bonds to the amino groups are shown. The wedge in Figure 1 indicates that the amino group is oriented in front of the plane of the page. The dashes in Figure 2 indicate that the amino group is oriented behind the plane of the page.

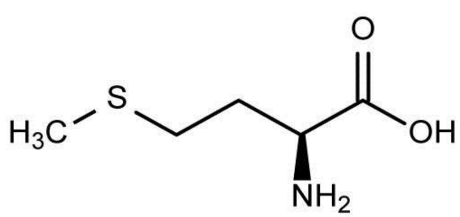

Figure 1. Molecular Structure of L-Methionine
Source: Helmenstine (undated)

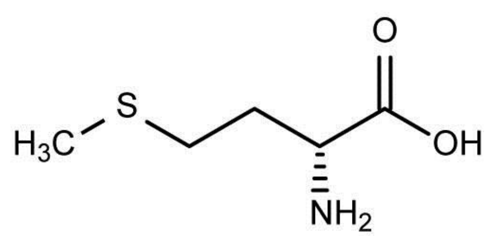

Figure 2. Molecular Structure of D-Methionine
Source: Helmenstine (undated)

<u>**Properties of the Substance**</u>:

Methionine is typically found as a white solid or white crystalline powder. Methionine is asymmetric, forming both an L- and a D- enantiomer (i.e., molecules with the same formula, but different three-dimensional shapes). It is available in its natural L- or D- forms, or as a synthetic (not present in nature), racemic mixture, DL-methionine (i.e., a mixture with equal portions of the two enantiomers). While one author found that both the D- and L- enantiomers were equally utilized in animals (Writland and Rose, 1950), another indicated that L-methionine is more efficiently utilized in the human body than the D- or the DL- forms (Kies et al., 1975). The L- enantiomer is the only form of methionine petitioned for use in organic handling because the petitioner (the International Formula Council) is requesting its approval for use in infant formula, and L-methionine is the only form allowed for use in infant formula (see 21 CFR 172.320). This report summarizes information for L-methionine only, unless specified otherwise. General references to "methionine" in this technical report refer to any of its forms.

L-methionine is soluble in water, methanol, alkali solutions, and mineral acids, and is slightly soluble in ether. It is stable under normal temperature and pressure, but is incompatible with strong oxidizing agents (Acros Organics, 2009). Toxic decomposition products of L-methionine include nitrogen oxides, carbon monoxide, oxides of sulfur, and carbon dioxide (Pestell Minerals and Ingredients, 2008). Physicochemical properties of L-methionine are summarized in Table 1.

Table 1. Physicochemical Properties of L-Methionine

Physical or Chemical Property	Value[a]
Physical state	Solid
Appearance	White crystalline powder
Odor	Characteristic
Molecular weight (g/mol)	149.21
Boiling point	NA
Melting point	281°C
Solubility in water (g/L)	30 (20°C)
Vapor pressure (hPa)	<0.0000001
Density (g/cm^3)	1.34

[a]Sources: ChemIDplus Lite (2011); Pestell Minerals and Ingredients (2008)

<u>Specific Uses of the Substance</u>:

Methionine is an essential amino acid that cannot be synthesized by the body; thus, it is used primarily as a dietary supplement in humans and a feed additive in livestock. Physiologically, methionine is required for nitrogen balance, cell metabolism, protein formation, and growth (Brosnan and Brosnan, 2006). A number of soy-based baby formulas are supplemented with L-methionine because soy formula (unlike milk-based formula or breast milk) does not provide adequate levels of methionine to ensure adequate growth, nitrogen balance, and plasma albumin concentrations (Agostoni et al., 2006). Brands of soy formula supplemented with L-methionine include Baby's Only Organic (Nature's One, 2007), Earth's Best Organic (2011), and Vermont Organics (2011). Methionine is also used to supplement some pet foods, but often with DL-methionine rather than L-methionine (Regal Pet Foods, undated; Healthwise, undated). Some organic pet foods also contain DL-methionine supplements, including Newman's Own brand adult cat formulas (Newman's Own Organics, undated). L-methionine may also be used as a supplement for pets in tablet form (NuVet, undated). Urinary tract problems in cats may also be treated with L-methionine supplementation (Funaba et al., 2001; Stanford Cat Network, undated).

Methionine may also be used for therapeutic purposes in humans. Because L-methionine can help balance pH, it may be used to treat urinary tract infections. It may also be used to treat acute pancreatitis and Parkinson's disease, and studies have shown it may be able to reduce toxic acetaldehyde levels after ethanol ingestion (Fugakawa, 2006; Atmaca, 2004).

<u>Approved Legal Uses of the Substance</u>:

Synthetic L-methionine 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). L-methionine has been petitioned for use in infant formula, but it may also be added to other foods, such as pet foods, or used as a dietary supplement.

Synthetic DL-methionine is currently included on the National List (7 CFR 205.603(d)) for use in organic livestock production as a feed additive. However, a "step-down" measure was established to reduce the amount of synthetic methionine allowed in feed. Until October 1, 2012, the following maximum levels of synthetic methionine per ton of feed are allowed—4 pounds for laying chickens, 5 pounds for broiler chickens, and 6 pounds for turkeys and all other poultry. The NOSB has recommended that, after October 1, 2012, the allowed levels of methionine be reduced to 2 pounds for laying chickens, 2 pounds for broiler chickens, and 3 pounds for turkeys and other poultry through October 1, 2015 (76 FR 13501). As of the date of this publication, the NOP has not published regulations to implement the stepdown provisions that will take effect after October 1, 2012.

Methionine (in either L- or DL- forms) is considered generally recognized as safe (GRAS) for animal consumption, but not for human consumption. However, L-methionine is regulated as a human nutrient/dietary supplement and is allowed as a special nutritional and dietary food additive for human consumption (21 CFR 172.320). DL-methionine and *N*-acetyl-L-methionine (CAS Number 65-82-7) also are approved by FDA for use as food additives, but regulations explicitly say they are not to be used in infant feed formulas (see 21 CFR 172.320 and 21 CFR 172.372).

FDA regulations (21 CFR 107.100[f]) on the nutrient requirements of infant formula stipulate that the biological quality of infant formula protein must be equivalent to or better than that of casein, a protein that comprises roughly 80% of cow milk and 60% of human milk. Because adequate methionine intake is essential for the production of cysteine (Brosnan and Brosnan, 2006), these two sulfur amino acids are often measured in relation to each other. Casein proteins have a higher content of methionine in relation to cysteine than soy protein (Dudásová and Grancicová, 1992), indicating that soy-based infant formulas must be supplemented to maintain adequate sulfur amino acid content. L-methionine is the only form of methionine permitted for use in infant food per FDA regulations (21 CFR 172.320). Studies in animals have shown that supplementation with methionine improved the quality of soy protein to be equal with that of casein in rat assays and to about 85% the quality of casein in guinea pigs (Fomen et al., 1979). In a human study, infants consuming unsupplemented soy protein formulas had less weight gain per 100 kcal, lower serum concentrations of albumin, and greater serum urea nitrogen compared with infants receiving breast milk, cow milk-based formula, or L-methionine-supplemented soy-based formula (Fomen et al., 1979).

Action of the Substance:

Methionine is classified as an essential amino acid because it is required in the diet for cell growth, protein formation, and cell metabolism, but cannot be biologically produced (Brosnan and Brosnan, 2006). Cysteine, another important amino acid, is synthesized from methionine, and adequate methionine intake is essential for adequate production of cysteine (Brosnan and Brosnan, 2006). In humans, L-methionine is more efficiently utilized in the human body than the D- or the DL- forms (Kies et al., 1975). Kies et al. (1975) found that more methionine was excreted in the urine when humans were given D- or DL-methionine than when they received L-methionine supplements.

Combinations of the Substance:

Methionine is a precursor to cysteine, and the amount needed in the diet depends on the amount of cysteine already present. Requirements for methionine are frequently cited in terms of methionine + cysteine because methionine is converted in the body (through several steps) to cysteine as needed (Brosnan and Brosnan, 2006).

L-methionine is sometimes combined with other nutrients or vitamins in dietary supplements. For example, Nature's Plus markets a L-methionine supplement with vitamin B6 (Vitamin Shoppe, 2012). Vitamin B6 is allowed in organic handling per 7 CFR 205.605(b), which permits the use of "nutrient vitamins and minerals, in accordance with 21 CFR 104.20." Specifically, vitamin B6 may be added to food at levels provided in 21 CFR 104.20(d)(3). It should also be noted that oral supplements of s-adenosyl-l-methionine (SAM), derived from L-methionine through a metabolic pathway called the one-carbon cycle, is a commonly-used dietary supplement and treatment for conditions such as depression (Mischoulon and Fava, 2002). SAM does not appear on the National List (7 CFR 205.605) and it has not been approved by the FDA.

L-methionine 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).

No information could be found regarding whether or not raw L-methionine formulations contain preservatives or carriers. Many dietary supplements (in capsule form) contain additives such as stearic acid, magnesium stearate, silica, or gelatin, but formulations vary by manufacturer. Certain brands claim not to contain preservatives, artificial flavors, or colors (Vitamin Shoppe, 2012).

Status

Historic Use:

Supplementation of infant formula with L-methionine began in the 1970s (AAP, undated).

The history of the legal use of synthetic L-methionine in organic handling/processing has revolved around uncertainty over the nutritional status of L-methionine because it is neither a vitamin nor a mineral. In 1995, the National Organic Standards Board (NOSB) made the following recommendation in "The Use of Nutrient Supplementation in Organic Foods" (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 at 7 CFR 205.605(b) permits the use of "nutrient vitamins and minerals, in accordance with 21 CFR 104.20" (USDA, 2011). 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-methionine 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-methionine. The NOP recently published a proposed rule that would amend the National List cross-reference to the FDA regulation 21 CFR 104.20. The proposed rule indicates that L-methionine is not among the substances allowed in non-milk based infant formulas as required by 21 CFR 107.100 (USDA, 2012). See "OFPA, USDA Final Rule" for more information.

OFPA, USDA Final Rule:

Synthetic and nonsynthetic L-methionine are 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-methionine. However, due to a previous misinterpretation of the regulations, some organic infant formulas do contain L-methionine and other nutrient additives (Nature's One, 2007; Vermont Organics, 2011; Earth's Best Organics, 2011). To resolve the misinterpretation, NOP published a proposed rule in January 2012 (77 FR 1980) that would not allow the use of nonrequired nutrients such as L-methionine as an ingredient in organic products, including organic food and organic infant formula, unless the NOSB issues recommendations to add it to the National List and such recommendations are codified through rulemaking. If promulgated as a final rule, this amendment would clarify that L-methionine is not allowed under the current annotation for required vitamins and minerals (USDA, 2012).

<u>International</u>:

L-methionine 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-methionine for nutritional purposes.

The Codex Alimentarius Commission lists L-methionine as an acceptable ingredient in the Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants. It is also an accepted ingredient in Food for Special Medical Purposes other than Infant Formula (Codex Alimentarius Commission, 2011). Section 3.5 of the Codex Standards for organically-produced 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 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-methionine does not appear on the list of "certain products and substances for use in production of processed organic food referred to in Article 27(1)(a)" in Annex VIII of EC No. 889/2008. However, per Directive 2006/141/EC and EC No. 1243/2008, infant formula must contain an identical amount of certain nutrients as is available in human breast milk (including 29 mg/100 kcal of methionine) suggesting that the EU would allow the use of L-methionine supplements in organic milk- and soy-based infant formulas.

The International Federation of Organic Agriculture Movements (IFOAM) does not list L-methionine within its "Norms for Organic Production and Processing" 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.*

L-methionine does not appear on the list of approved food additives in the Japan Agricultural Standard (JAS) for Organic Processed 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 information is provided in the standard.

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-methionine may be isolated from naturally-occurring sources, produced from genetically-engineered organisms, or synthesized through many processes. While methionine has been produced by fermentation in the laboratory, racemic mixtures of D- and L-methionine (i.e., DL-methionine) are usually produced entirely by chemical methods (Araki and Ozeki, 1991). Most L-methionine is produced from synthetic DL-methionine, and DL-methionine can be produced in following ways:

- Reaction of acrolein with methyl mercaptan in the presence of a catalyst (Fong et al., 1981);
- Reaction of propylene, hydrogen sulfide, methane, and ammonia to make the intermediates acrolein, methylthiol, and hydrocyanic acid (DeGussa, 1995; 1996);
- Use of the Strecker synthesis method with α-methylthiopropionaldehyde as the aldehyde (Fong et al., 1981); or
- Reaction of 3-methylmercaptopropionaldehyde with ammonia, hydrogen cyanide, and carbon dioxide in the presence of water in three reaction steps (Geiger et al., 1998).

In general, L-methionine is produced from DL-methionine via optical resolution resulting in separation into the D- and L- enantiomers (Ajinomoto Corporation, 2012) or by acetylation of synthetic DL-methionine and subsequent enzymatic selective deacetylation of the N-acetylated L-methionine (Usuda and Kurahashi, 2010). Because much of the DL-methionine supply is synthesized using chemical methods, the L-methionine produced from it is also synthetic. While nonsynthetic L-methionine can be produced by fermentation, there are no commercial sources available that use this method (Kumar and Gomes, 2005). See Evaluation Question #2 for more information.

<u>Evaluation</u> <u>Question #2:</u> 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)).

Most commercially available L-methionine is synthetic based on the manufacturing processes described in Evaluation Question #1. As described above, most L-methionine is produced from DL-methionine using optical resolution resulting in separation into the D- and L- enantiomers (Ajinomoto Corporation, 2012) or by acetylation of synthetic DL-methionine and subsequent enzymatic selective deacetylation of the N-acetylated L-methionine (Usuda and Kurahashi, 2010).

It is possible to produce nonsynthetic forms of L-methionine through fermentation; however, there are no known commercial sources that currently employ the bioproduction of methionine (Kumar and Gomes, 2005; Usuda and Kurahashi, 2005). This might be partially due to the complexity of the methionine biosynthetic pathway and, because methionine is vital to cellular function, it is highly regulated by the microorganisms that produce it. The realization of large-scale fermentation production of L-methionine will likely require genetic modifications of microorganisms to deregulate some of these controls and allow for significant excretion of methionine (Usuda and Kurahashi, 2010). Bacterial strains do mutate naturally to "overproduce" methionine, although screening procedures have been designed to allow for isolation of the overproducer mutants (Kumar and Gomes, 2005). However, it is likely that the yields from unmodified bacteria would be too low for this to be a viable L-methionine source, and genetically modified bacteria would be required to produce commercially viable supplies of L-methionine (Kumar and Gomes, 2005). A recent patent application for a method to produce L-methionine by fermentation was available online (Usuda and Kurahashi, 2010). The patent was submitted by Ajinomoto Corporation, which produces L-methionine as one of its "small pack amino acids." According to its website, all of these small pack amino acids are made using biofermentation processes (Ajinomoto Corporation, 2011). However, the patent indicates that genetic modifications of microorganisms are required, suggesting the product would not be allowed for use in organic agriculture. In April 2011, Arkema chemical company announced plans to open a biofermentation plant to produce L-methionine from raw plant sources. The plant is slated to "come on stream" by the end of 2013 (Arkema, 2011). It is unclear if this production system requires genetic modification of bacterial strains.

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

As described in Evaluation Question #2, there are no known nonsynthetic sources of L-methionine commercially available at this time. While L-methionine can be produced through fermentation processes of microorganisms, it is likely that the yields from nonmodified bacteria would be too low for this to be a viable L-methionine source at the commercial scale. Genetically-modified bacteria would likely be required to produce commercially viable supplies of methionine (Kumar and Gomes, 2005).

Nonsynthetic methionine is found naturally in foods such as rice; rapeseed; soybean meal; sunflower, safflower, and sesame seeds; flax; alfalfa; grass; corn; wheat; and peas (Fanatico, 2010). Levels of methionine vary by food. For example, corn has only 0.17% methionine while soybean meal has 0.64% methionine. Methionine is also found naturally in animal protein from insects, meat, and dairy products, which are permitted in organic agriculture. Thus, natural methionine can be obtained through the diet from various high-methionine foods. However, methionine is not present in high volumes in unsupplemented soy infant formulas, and since many infants rely solely on infant formula, dietary methionine intake is not adequate from unsupplemented soy formula alone (Fomen et al., 1979).

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?

Methionine (in either the L- or DL- form) is generally recognized as safe (GRAS) by the U.S. Food and Drug Administration (FDA) for animals when used in accordance with good manufacturing and feeding practice (21 CFR 582.5475). While it is not GRAS for human consumption, L-methionine may be used as a nutrient added to foods in accordance with 21 CFR 172.320. The technical function of L-methionine is as a dietary supplement (see Approved Legal Uses for the Substance).

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-methionine has preservative properties.

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-methionine is not used to 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-methionine supplementation can be used to improve the nutritional quality of food. As stated in "Specific Uses of the Substance," methionine cannot be produced by the body and must be supplied via the diet (Brosnan and Brosnan, 2006). While many foods naturally contain methionine, certain populations, such as infants requiring a diet of soy infant formula only, will not obtain adequate methionine from diet (Fomen et al., 1979). Most soy-based infant formulas are supplemented with L-methionine with the intention of improving the nutritional quality of the formula.

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-methionine was identified. It should be noted, however, that makers of dietary supplements can voluntarily apply for verification by U.S. Pharmacopeia (USP), which has a strict set of 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-methionine supplement that is USP verified should not contain metals at levels higher than 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)).

Synthetic L-methionine used as a nutritional supplement can enter the environment through waste streams from its production, use, and disposal. L-methionine has a relatively low vapor pressure, indicating that L-methionine present in soil or water is not likely to evaporate into air. L-methionine is highly mobile in soil, and research has shown that most of the L-methionine in soil breaks down in about 16 days. L-methionine can exist as a vapor or particulate in the air. Airborne L-methionine vapor will be degraded in the atmosphere with a half-life of about 7.5 hours. Methionine is also found naturally in water from the metabolism of proteins in aquatic organisms. The potential for bioconcentration of L-methionine in aquatic organisms is expected to be low based on its low bioconcentration factor (calculated by dividing the concentration of L-methionine in the tissue over the concentration of L-methionine in water). L-methionine will degrade in water from exposure to sunlight (HSDB, 2010).

Synthetic production of DL-methionine (from which L-methionine is usually derived) involves a number of toxic source chemicals (e.g., methyl mercaptan [CH_3SH] and acrolein, the chemicals used as reactants in the production of DL-methionine) and intermediates that also have the potential to enter the environment through waste streams or accidental releases.

The majority of acrolein releases reported to the Toxics Release Inventory (TRI) in 2010 were air releases (274,701 pounds of point-source releases); only 140 pounds of acrolein was released to surface water as reported by the acrolein manufacturing and processing facilities required to report (U.S. EPA, 2011). In 2010, 355,499 pounds of acrolein were disposed of in underground injection wells (U.S. EPA, 2011). Methyl mercaptan is not currently reported to TRI, so it is unclear how much is released through production wastestreams. Occasional accidental releases of both of these chemicals have been reported, including a 2001 spill in Michigan in which a railroad car fractured and separated, releasing methyl mercaptan that subsequently ignited (NTSB, 2001). Eleven accidental releases of acrolein were reported to the NRC (National Response Center; responsible for tracking chemical spills in the U.S. as required by law) in 2011, with releases ranging from unreported amounts to 43 pounds (NRC, 2011). The NRC reported sixteen releases of methyl mercaptan in 2011 ranging from unknown amounts to 2150 pounds (NRC, 2011).

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)).

Humans must acquire a certain level of methionine from the diet because it is an essential amino acid required for cell growth and it cannot be endogenously produced. Required intake has been estimated to be 5–13 mg/kg-day as part of a 13–21 mg/kg-day intake of total sulfur amino acids (Fugakawa, 2006). The L- form of methionine is used in human medicine as a dietary supplement and for a variety of therapeutic purposes, including pH and electrolyte balancing. It may also be used to treat acute pancreatitis and Parkinson's disease, and studies have shown it may be able to reduce toxic acetaldehyde levels after ethanol ingestion (Fugakawa, 2006; Atmaca, 2004). However, methionine has been called the most toxic of amino acids (Benevenga and Steele, 1984 in Garlick, 2004) and it can be toxic to humans at high doses. Methionine may cause nausea, vomiting, dizziness, irritability, and liver dysfunction at high doses (e.g., 5 or 10 g/day) and should be used with caution in patients with severe liver disease (Reynolds, 1996). Most of these symptoms are short term and do not cause permanent damage in otherwise healthy individuals (Garlick, 2006). Large doses of methionine (e.g., 11.3 g/day) may induce acidosis in humans, which, over extended periods, could cause negative nitrogen balance and decreased synthesis of muscle protein and serum albumin (Garlick, 2006). Note that dietary supplements usually contain around 500 mg (0.5 g) of L-methionine and are taken once daily (Vitamin Shoppe, 2012). In volunteers given doses of 4–40 g/day of L- or DL-methionine by mouth for 2 weeks, 7 of 11 patients with schizophrenia experienced exacerbated psychotic symptoms (Antun et al., 1971 in Garlick, 2004; Garlick, 2006). In addition, animal studies indicate that methionine (at doses of ~5% of diet) may cause homocysteinemia, which is correlated with cardiovascular disease. This may be a concern for long-term users of methionine as a supplement (Garlick, 2004). These adverse effects are thought to be associated with the production of methanethiol-cysteine–mixed disulfides in the body.

Larger than normal doses of methionine in infant formula have led to cases of hypermethioninemia (excess methionine in the blood). In a review article, Garlick (2006) described a case in which 10 infants consuming formula high in methionine (intake was estimated at 125–507 mg/kg-day of methionine compared with the average intake of 62–97 mg/kg-day from typical formula) experienced hypermethioninemia. However, no long-term effects were reported in these infants. The infant formula involved in these cases has since been reformulated (Garlick, 2006).

Occupational exposure to the reactants used to manufacture DL-methionine and subsequently, L-methionine, may also affect health. Methyl mercaptan reacts with water, steam, or acids to produce flammable and toxic vapors (Sax, 1984). Methyl mercaptan fires are highly hazardous and can cause death by respiratory paralysis (U.S. EPA, 1987). Another potential component of methionine production is acrolein. Acrolein is an eye and respiratory tract irritant (OEHHA, 2000) listed as a federal air pollutant by U.S. EPA and is 1 of 33 pollutants of "greatest concern for exposure and health effects" (U.S. EPA, 2003).

Evaluation Information #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 that could serve as alternatives to L-methionine for use in dietary supplements, infant formulas, and foods were identified. While infants could be fed organic milk-based formulas, which naturally have sufficient L-methionine content, rather than soy-based formulas, this would not be an option for infants with milk allergies.

Certain foods naturally contain methionine. Methionine is contained at lower levels in sunflower, safflower, and sesame seeds; corn; wheat; rice; and peas. It is found at higher levels in animal protein from insects, fish, and dairy products (Fanatico, 2010). These foods can be obtained from organic sources. It may be possible for certain people to obtain adequate methionine (and total sulfur amino acids) from a balanced diet without supplementation. However, populations such as infants requiring soy formula (with low methionine content) and vegetarians may not obtain adequate methionine from their diet (Fomen et al., 1979).

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