Isopropanol

Livestock

Identification of Petitioned Substance

Chemical Name:
2-Propanol

Other Name:
Isopropanol
Isopropyl Alcohol

Trade Names:
Rubbing Alcohol

CAS Numbers:
67-63-0

Other Codes:
200-661-7 (EINECS No.)

Summary of Petitioned Use

The National Organic Program (NOP) final rule currently allows the use of isopropanol in organic livestock production under 7 CFR 205.603(a)(1)(ii) as a surface disinfectant only. Although not explicitly stated in the Final Rule, isopropanol is prohibited as a feed additive in organic production. Isopropanol is also allowed for use in organic crop production under 7 CFR 205.601(a)(1)(ii) as an algicide, disinfectant, and sanitizer, including irrigation systemic cleaning. In this report, updated and targeted technical information for isopropanol is compiled to augment the original 1995 Technical Advisory Panel (TAP) Report for Alcohols, which included methanol, ethanol, and isopropanol.

Characterization of Petitioned Substance

Composition of the Substance:

Isopropanol, or isopropyl alcohol, is an organic compound consisting of three carbon atoms, eight hydrogen atoms, and one oxygen atom. The exact composition of industrial isopropanol products generally depends on the isopropanol concentration, purity, and intended uses. High purity, anyhydrous (water free) isopropanol consists of only the pure substance. Isopropanol may also be diluted with various quantities of water for industrial, academic, and medical/antiseptic uses; for example, commercial rubbing alcohol solutions used as antiseptics typically contain 70 percent isopropanol by volume. See "Combinations of the Substance" below for additional information regarding the formulation of consumer products containing isopropanol and the NOP status of principal additives.

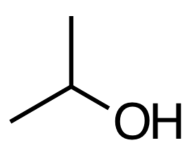

Figure 1. Isopropanol structural formula

Source or Origin of the Substance:

Chemical synthetic procedures are employed in the commercial production of isopropanol used in the preparation of consumer use disinfectants, industrial solvents, and specialty chemicals. Specifically, indirect and direct methods for the hydration of petroleum-derived propylene ($CH_3CH=CH_2$) are the two primary commercial processes for the production of isopropanol. In addition, smaller amounts of industrial isopropanol are generated through the hydration of acetone [$(CH_3)_2C=O$] over transition-metal catalysts (Papa, 2011; Merck, 2006). A variety of methods are also available for the fermentative production of isopropanol from carbon sources, such as starch, sugar, and cellulose, using genetically engineered yeast and bacteria (Papa, 2011). However, most of these biological fermentation methods are limited to laboratory scale production levels and are geared toward production of isopropanol as a biofuel. See Evaluation Questions #2 and #3 for a detailed discussion of the synthetic and fermentative methods potentially used in commercial isopropanol production.

Properties of the Substance:

Isopropanol is a volatile, flammable, colorless liquid with the molecular formula $(CH_3)_2CHOH$. A summary of the chemical and physical properties of pure (absolute) isopropanol is provided below in Table 1.

Table 1. Chemical and Physical Properties of Isopropanol

Property	Value/Description
Color	Clear, colorless
Physical State	Mobile liquid
Molecular Formula	$(CH_3)_2CHOH$ (C_3H_8O)
Molecular Weight, g/mol	60.09
Freezing Point, ºC	–89.5
Boiling Point, ºC	82.5
Density, g/mL	0.785
Dissociation constant (pK_a)	17.1
Solubility in water, 25 ºC	Infinitely soluble at 25 ºC
Solubility in organic solvents	Miscible in many organic solvents (ethanol, diethyl ether, chloroform, benzene, and acetone); insoluble in salt solution.
Viscosity at 20 ºC, mPa•s	2.04
Soil Organic Carbon-Water Partition Coefficient (K_{oc}), mL/g	1.5 (Mobile in soils)
Aerobic Soil Half-life (DT_{50})	Literature suggests DT_{50} is 1–7 days
Hydrolysis	Stable to hydrolysis
Photodegradation	Isopropanol is subject to oxidation in air by hydroxyl radical attack; direct photolysis is not expected to be an important transformation process.
Octanol/Water Partition Coefficient (K_{ow})	1.12
Vapor Pressure, mm Hg	45.4
Henry's Law Constant, atm•m^3/mol	8.1×10^{-6}

Data Sources: Sigma Aldrich, 2013; HSDB, 2012; Papa, 2011; UNEP, 1997; Howard, 1991.

Specific Uses of the Substance:

Isopropanol is used for a variety of industrial and consumer purposes, ranging from chemical and solvent applications to medical and consumer usage. The major uses of isopropanol have been divided into five overall categories: solvent applications; chemical intermediate in synthesis; household, cosmetic, personal-care products; pharmaceuticals; and production of acetone (Dow, 2011). In the following paragraphs, targeted technical information is provided for the use of isopropanol in organic livestock and crop production as well as the broader applications presented below in Figure 2.

Agricultural uses of isopropanol include the disinfection of production tools and surfaces and topical antisepsis during medical treatments. Livestock producers may use alcohol (i.e., isopropanol and/or ethanol) solutions for sanitizing and disinfecting surfaces (e.g., production implements, troughs, and floor drains) and during medical treatments as a topical disinfectant (Jacob, 2013; Dvorak, 2008). Indeed, a protocol for the disinfection of methicillin-resistant *Staphylococcus aureus* (MRSA) on sows and their piglets using alcohol solutions was recently reported in the open literature (Pletinckx, 2013). Rubbing alcohol is also used to disinfect production implements such as livestock tagging applicators (OSU, undated). Commercial isopropanol products are available for "external use only as an antiseptic, disinfectant and rubefacient in cattle, horses, sheep, swine, dogs and cats" (AgriLabs, undated). Antiseptic products containing a mixture of ethanol and isopropanol are available for use on cattle, sheep and swine; for details, see the product label for Barrier® Livestock Wound Care (NIH, 2013). Regarding crop production, isopropanol may be effectively used to decontaminate the lines of irrigation systems and remove bacteria, viruses and fungi from cutting tools (Benner, 2012).

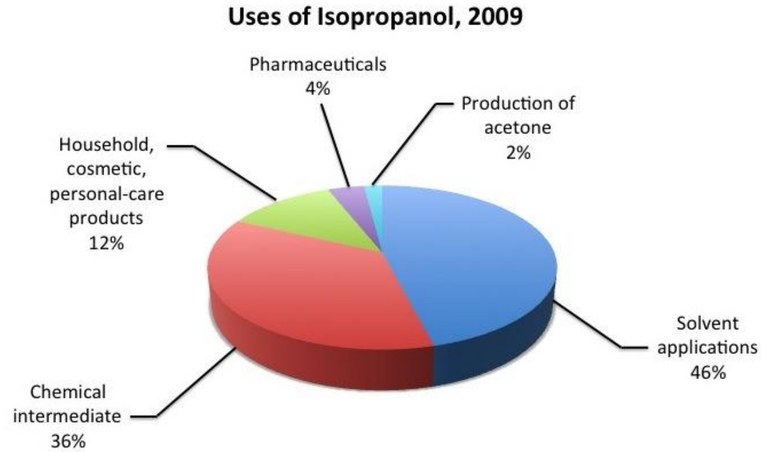

Figure 2. Adapted from Dow, 2011.

In addition to antimicrobial uses in agriculture, isopropanol is also widely used in commercial and household products including hand sanitizers, medical disinfectants, and flea/tick pesticide products. Alcohols, including isopropanol and ethanol, are capable of providing rapid broad-spectrum antimicrobial activity against vegetative bacteria, viruses and fungi, but lack activity against bacterial spores (McDonnell, 1999). Indeed, the CDC recommends against the use of isopropanol or ethanol as the principal sterilizing agent because these alcohols are insufficiently sporicidal (i.e., spore killing) and cannot penetrate protein-rich materials (CDC, 2008). Notwithstanding these limitations, isopropanol has been used to disinfect thermometers, hospital pagers, scissors, and stethoscopes. Commercial towelettes and other wipes saturated with isopropanol have also been used to disinfect small surfaces in medical settings. As a general disinfectant, isopropanol is generally applied through surface wipes, sprays, mop-on, sponge-on, wipe-on or pour-on treatments, and by immersion. Isopropanol is also used to disinfect closed commercial/industrial water-cooling systems (EPA, 1995). Studies have indicated that isopropanol is about twice as effective as ethanol as a surface disinfectant (Logsdon, 2000).

Large volumes of isopropanol are used for purposes beyond disinfection and other pesticide applications in agricultural, household, and medical settings. As a solvent, isopropanol is used in acrylic acid and epoxy resins, ethyl cellulose, natural resins, gums as well as some paints, inks, and essential oils. Isopropanol is also a chemical feedstock used in the production of acetone, isopropylamines, isopropylacetates, and a number of other specialty chemicals (Dow, 2011). In addition, isopropanol is used in the production of cosmetic base materials and pesticide carriers and the extraction of fatty acids from vegetable oils at moderate to low temperature (Papa, 2011). Other applications of isopropanol are as an octane enhancer, carburetor anti-icing additive, and methanol co-solvent in motor gasoline blends (Papa, 2011).

Approved Legal Uses of the Substance:

United States Food and Drug Administration

The United States Food and Drug Administration (FDA) regulations allow a number of uses for isopropanol in food preparation/processing for humans and animals. Regarding the focus of this report, isopropanol may be used in sanitizing solutions for food processing equipment and food contact surfaces, including containers for holding milk (21 CFR 178.1010). Isopropanol may also be used in inks for marking food supplements, gum, and confectionery as well as a diluent in color additive mixtures for drug use (21 CFR 73.1). The FDA further authorizes isopropanol as an indirect food additive for use as a component of adhesives only (21 CFR 175.105).

As an additive permitted for direct addition to food for human consumption (FDA, 2013), isopropanol may be used as a solvent in the extraction of hops and therefore present in modified hop extract at a concentration of 250 parts per million (21 CFR 172.560). In addition, isopropanol is a food additive permitted for direct addition to food for human consumption as a synthetic flavoring substance or adjuvant (21 CFR 172.515). The following conditions must be met for the use of isopropanol as a flavoring substance/adjuvant: (1) the minimum quantity of isopropanol is used to produced the desired effect, and

(2) isopropanol must be used alone or in combination with flavoring substances/adjuvant generally recognized as safe (GRAS) in food or otherwise sanctioned for such use.

A number of FDA-approved applications exist for isopropanol as a secondary direct food additive (i.e., substance required during the manufacture or processing of a food) in food for human consumption. For example, isopropanol may be used as a component of defoaming agents for the processing of beet sugar and yeast (21 CFR 173.340). Isopropanol is legally used as a solvent in the extraction of various conventional agricultural commodities and may therefore be present under specified conditions in the following extracts (21 CFR 173.240):

- Spice oleoresins as a residue from the extraction of spice, at a level not to exceed 50 parts per million (ppm).
- Lemon oil as a residue in production of the oil, at a level not to exceed six ppm.
- In hops extract used in the manufacture of beer as a residue from the extraction of hops at a level not to exceed two percent by weight, provided that:
  - The hops extract is added to the wort before or during cooking in the manufacture of beer,
  - The label of the hops extract specifies the presence of isopropyl alcohol and provides for the use of the hops extract only before or during cooking in the manufacture of beer.

United States Environmental Protection Agency

The United States Environmental Protection Agency (US EPA) regulates all non-food applications of isopropanol, including its use in antimicrobial products and insecticides. According to the Reregistration Eligibility Decision (RED) for Aliphatic Alcohols, isopropanol and ethanol were registered in the US as early as 1948 as active ingredients in indoor disinfectants (US EPA, 1995). Approximately 30 isopropanol products were registered for use as hard surface treatment disinfectants, sanitizers and mildewcides as of 2012 (US EPA, 2012b). In addition to its antimicrobial applications, isopropanol is also used as an adjuvant in several pesticide products such as insecticides, acaricides, and repellents (US EPA, 1995).

Isopropanol is also exempt from the requirement of a tolerance due to its minimal risk status. Specifically, residues of isopropanol resulting from its use as an active and/or inert ingredient in a pesticide chemical formulation, including antimicrobial pesticide products, are exempt from the requirement of a tolerance (40 CFR 180.950). As stated in the 2006 Federal Register Notice (US EPA, 2006), this rule effectively replaced the existing tolerance exemptions for isopropanol used as an inert ingredient pre- and post-harvest (40 CFR 180.910) and an inert ingredient applied to animals (40 CFR 180.930). As of 2012, there are approximately 1200 pesticide products using isopropanol as an inert ingredient (US EPA, 2012b).

Action of the Substance:

Isopropanol functions as a disinfectant through the dissolution of lipid membranes and rapid denaturation of proteins. Because proteins are denatured more quickly in the presence of water, enhanced bactericidal activity is generally observed for mixtures of isopropanol and water when compared to concentrated isopropanol, which functions as a dehydrating agent (CDC, 2008; McDonnell, 1999). This crude observation provides qualitative support for the proposed mechanism, which relies heavily upon the ability of isopropanol to denature proteins. Isopropanol is able to effectively destroy many types of bacterial and viral cells due to this mode of action; however, it is ineffective against bacterial spores because the substance evaporates before it can effectively penetrate the membrane and lead to protein denaturation (CDC, 2008).

Combinations of the Substance:

Rubbing alcohol products containing isopropanol as the active ingredient are more common and contain fewer additives than ethanol-based products. Ethanol-based rubbing alcohol products are required by law to contain a certain amount of denaturing agents to render the disinfecting solution unpalatable for human consumption (ODN, 1993). Because isopropanol is not used in alcoholic beverages, denaturants are unnecessary in isopropanol-based rubbing alcohol products. Indeed, Material Safety Data Sheets (MSDS) for isopropanol-based rubbing alcohol products indicate that these solutions generally contain 70–90 percent isopropanol and 30–10 percent water (Science Lab, 2005; Lewis, 2003). It is important to note, however, that any alcohol-based topical antiseptics may include low levels of other biocides (e.g., chlorhexidine), which remain on the skin following isopropanol evaporation, or excipients, which extend the lifetime of isopropanol on skin and thus increase product efficacy (McDonnell, 1999). Further, antiseptic products consisting primarily of ethanol with small amounts of isopropanol as the active ingredients will likely contain denaturing agents such as denatonium benzoate (NIH, 2013).

Status

Historic Use:

In 1920, Standard Oil became the first company to produce isopropanol on an industrial scale. However, it was used primarily as an intermediate in the synthesis of acetone, not as the active ingredient in rubbing alcohol (Green, 2003). Although historical information documenting the use of isopropanol-based disinfectants is unavailable, it is likely that naturally-derived alcohol (i.e., ethanol) was the principal disinfectant prior to the advent of chemical sanitizers, including quaternary ammonium salts, peroxides, chlorine dioxide, bleach and synthetic alcohols (i.e., isopropanol and ethanol). Modern sanitation standards and understanding regarding the spread of deleterious microorganisms through contaminated farm instruments likely increased the agricultural use of isopropanol, ethanol, and other disinfectants throughout the twentieth century.

Organic Foods Production Act, USDA Final Rule:

No mention of alcohol, isopropanol, or isopropyl alcohol is made in the Organic Foods Production Act of 1990 (OFPA). Isopropanol is an allowed synthetic substance on the National List for organic livestock production when used as a disinfectant only (7 CFR 205.603(a)(1)(ii)). In addition, isopropanol is an approved synthetic substance in organic crop production when used as an algicide, disinfectant, and sanitizer, including irrigation cleaning systems (7 CFR 205.601(a)(1)(ii)). The current USDA organic regulations also permit the use of isopropanol as an inert ingredient in pesticide products due to its inclusion on EPA List 4B (7 CFR 205.601(m) and 205.603(e)(1)). According to the 1995 Technical Advisory Panel Report, "alcohols are allowed as solvents and carriers in brand name products with allowed active ingredient(s). Also as disinfectant and in plant extracts" (USDA, 1995).

International

A small number of international organizations provide guidance on the application of synthetic isopropanol in organic livestock and crop production as well as the processing of organic foods. Among these are the Canadian General Standards Board and the International Federation of Organic Agriculture Movements (IFOAM). Below, international regulations and standards regarding the use of isopropanol in any form of organic production are summarized. Allowed uses of the related aliphatic alcohol, ethanol, are provided when technical information related to isopropanol is unavailable.

Canadian General Standards Board

Canadian organic production standards permit the use of isopropanol for a number of agricultural applications. According to the "Organic Production Systems Permitted Substances List," nonsynthetic and synthetic sources of isopropanol may be used as a cleaner, disinfectant or sanitizer on food contact surfaces. It is further stipulated that the substance must be removed from food contact surfaces prior to resuming normal production activities. Isopropanol is also allowed in organic livestock production as a disinfectant used to "maintain or restore the well being of an animal" (CAN, 2011a). The Canadian General Principles and Management Standards make specific mention of food-grade ethanol used to disinfect tapholes and tapping equipment in maple syrup procurement operations; however, isopropanol is not permitted for any purposes discussed in this guidance document (CAN, 2011b).

Codex Alimentarius

The Codex Guidelines do not provide any allowable uses for isopropanol in the production or processing of organically produced foods. However, ethanol is allowed under Annex 2 (table 2) of the Guidelines when mechanical, physical and biological methods are inadequate for pest control. Further, the Guidelines require that an organic certification body or authority recognize the need for any pest control treatments using ethanol. Ethanol is also listed as an allowed processing aid "which may be used for the preparation of products of agricultural origin." Specifically, ethanol may be used as a solvent in these preparatory operations (Codex, 2013).

European Economic Community Council

Isopropanol is not an allowed synthetic substance for organic production within the European Union. However, Commission Regulation (EC) No 889/2008 provides rules for two different uses of ethanol in organic production in European Union member states. Alcohol, likely referring to ethanol alone, may be used for cleaning and disinfecting livestock building installations and utensils under Annex VII of the regulations. In addition, Annex VIII stipulates the use of ethanol (not isopropanol) in Section B—Processing aids and other products, which may be used in the processing of ingredients of agricultural origin from organic production. This regulation specifically allows the use of ethanol as a solvent in the preparation of foodstuff of both plant and animal origin.

Japan Ministry of Agriculture, Forestry, and Fisheries

Japanese organic standards do not directly permit the use of isopropanol for any purpose in organic production or processing. In contrast, ethanol is allowed for use in several areas of organic production/processing. In lieu of information related to the use of isopropanol, technical information for ethanol is compiled in the following paragraph.

According to the Japanese standards for organic plant production, ethanol may be used in the processing, cleaning, storage, packaging and other post-harvest processes when physical or methods utilizing biological function are insufficient. The specific crop uses of ethanol are for (1) controlling noxious animals and plants, and (2) quality preservation and improvement (JMAFF, 2005a). Likewise, ethanol may also be used in the manufacturing, processing, packaging, storage and other processes associated with organic livestock feed when physical or methods utilizing biological function are insufficient for disease and pest control (JMAFF, 2005b). Similar provisions exist for the use of ethanol in the slaughter, dressing, selection, processing, cleaning, storage, packaging and other processes associated with organic livestock products. "Alcohols" are listed as allowed cleaning and disinfection agents for livestock housing; however, it is unclear whether isopropanol is allowed under this listing (JMAFF, 2005c). It should be noted that ethanol use is not permitted for the purpose of pest control for plants and agricultural products. For processed foods, ethanol may be used as an additive in the processing of meat products only (JMAFF, 2005d).

International Federation of Organic Agricultural Movements

Under the IFOAM Norms, isopropanol is an approved synthetic equipment cleaner and equipment disinfectant. Isopropanol is also an allowed synthetic substance for pest and disease control and disinfection in livestock housing (IFOAM, 2012). Because all commercial isopropanol is currently produced synthetically, natural sources of isopropanol are not considered in the IFOAM Norms.

Evaluation Questions for Substances to be used in Organic Crop or Livestock Production

<u>Evaluation Question #1: Indicate which category in OFPA that the substance falls under:</u> (A) Does the substance contain an active ingredient in any of the following categories: copper and sulfur compounds, toxins derived from bacteria; pheromones, soaps, horticultural oils, fish emulsions, treated seed, vitamins and minerals; livestock parasiticides and medicines and production aids including netting, tree wraps and seals, insect traps, sticky barriers, row covers, and equipment cleansers? (B) Is the substance a synthetic inert ingredient that is not classified by the EPA as inerts of toxicological concern (i.e., EPA List 4 inerts) (7 U.S.C. § 6517(c)(1)(B)(ii))? Is the synthetic substance an inert ingredient which is not on EPA List 4, but is exempt from a requirement of a tolerance, per 40 CFR part 180?

(A) There are a number of home, commercial and agricultural uses of isopropanol as a sanitizer and disinfectant. Therefore, isopropanol falls in the category of "equipment cleansers."

(B) Isopropanol may be considered an active or inert ingredient depending on the isopropanol concentration and intended use for a specific product (US EPA, 1995). As an inert, isopropanol is listed as "2-propanol" (CAS No. 67-63-0) on the US EPA List 4B—Other ingredients for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment (US EPA, 2004).

Isopropanol is also exempt from the requirement of a tolerance due to its low risk status. Specifically, residues of isopropanol resulting from its use as an active and/or inert ingredient in a pesticide chemical formulation, including antimicrobial pesticide products, are exempt from the requirement of a tolerance (40 CFR 180.950). As stated in the 2006 Federal Register Notice (US EPA, 2006), this exemption listing effectively replaced the former tolerance exemptions for isopropanol used as an inert ingredient pre- and post-harvest (40 CFR 180.910) and an inert ingredient applied to animals (40 CFR 180.930).

Evaluation Question #2: 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)).

Major commercial methods for the industrial production of isopropanol involve chemical synthesis from propylene and water. In addition, the hydrogenation of by-product acetone is practiced commercially for low volume isopropanol production. Other synthetic methods have been investigation in the laboratory but not fully developed to commercial scale. These include fermentation of certain carbohydrates, oxidation of propane, and hydrolysis of isopropyl acetate. For the purposes of this report, focus is given to commercial production methods currently in practice, with incorporation of relevant insights and developments from the independent literature. Technical information is compiled below for the three commercially relevant synthetic processes, as well as developments in the independent literature for the fermentative production of isopropanol.

Indirect Hydration

The indirect hydration, also known as the sulfuric acid process, was the only process used worldwide from 1920 until ICI developed an industrial direct hydration process in 1951 (Papa, 2011; Logsdon, 2000). Propylene ($CH_3CH{=}CH_2$) and water are the chemical feedstocks for isopropanol formation in the indirect process. Indirect hydration can tolerate lower purity streams of propylene from refineries and is therefore commercially employed to a greater extent in the United States compared to Europe.

In the indirect hydration process, C_3-feedstock streams from crude oil refinery off-gases containing 40–60 percent propylene ($CH_3CH{=}CH_2$) are subjected to sulfuric acid (H_2SO_4) to generate both isopropyl hydrogen sulfate [$(CH_3)_2CHOSO_3H$] and diisopropyl sulfate [$((CH_3)_2CHO)_2SO_2$] (Papa, 2011; Logsdon, 2000). These sulfate intermediates are then hydrolyzed with water to generate the desired product, isopropanol, and release sulfuric acid for further reaction cycles. The reaction mixture is neutralized using sodium hydroxide (NaOH) and distilled to afford pure isopropanol. Diisopropyl ether [$((CH_3)_2CH)_2O$] is the principal by-product formed via reaction of the intermediate sulfate esters with isopropanol, and is generally recycled back to the reactor for hydrolysis to isopropanol (Papa, 2011). Minor by-products (≤ 2 percent) include acetone, carbonaceous material, and polymers of propylene. See chemical equations below for step one (esterification) and step two (hydrolysis) in the indirect hydration process for isopropanol production (Figure 3).

Step 1. Esterification:

$$CH_3CH{=}CH_2 + H_2SO_4 \rightleftharpoons (CH_3)_2CHOSO_3H$$

$$(CH_3)_2CHOSO_3H + CH_3CH{=}CH_2 \rightleftharpoons ((CH_3)_2CHO)_2SO_2$$

Step 2. Hydrolysis:

$$(CH_3)_2CHOSO_3H + H_2O \rightleftharpoons (CH_3)_2CHOH + H_2SO_4$$

$$((CH_3)_2CHO)_2SO_2 + 2\,H_2O \rightleftharpoons 2\ (CH_3)_2CHOH + H_2SO_4$$

Figure 3. Chemical equations for indirect hydration (Logsdon, 2000).

Direct Hydration

Developed in 1951, the direct hydration process addressed many of the early problems associated with the indirect hydration method, including equipment corrosion from concentrated sulfuric acid, high energy costs, and air pollution (Papa, 2011; Logsdon, 2000). However, high purity propylene feedstock is required for this process. Direct hydration is predominantly employed in Europe for industrial isopropanol production, but to a lesser extent in the United States.

The acid-catalyzed direct hydration of propylene ($CH_3CH{=}CH_2$) to form isopropanol [$(CH_3)_2CHOH$] generally resembles the preparation of ethanol (CH_3CH_2OH) from ethylene ($H_2C{=}CH_2$) (Papa, 2011; Logsdon, 2000). Direct hydrations are conducted using high pressures and low temperatures over an acidic fixed-bed catalyst, which pushes the exothermic (heat releasing) equilibrium reaction toward the formation of isopropanol (eq 1). Three versions of the direct hydration process are practiced commercially today for isopropanol formation. One method feeds a mixture of propylene gas (92 percent purity) and liquid water to the top of a fixed bed reactor containing a sulfonated polystyrene ion-exchange resin catalyst and allows it to trickle downward. Another direct method reacts propylene (95 percent purity) and water (both gas and liquid phase) over a reduced tungsten oxide catalyst. The final method uses medium to high pressures of high purity propylene (~99 percent) with a tungsten oxide – silicon dioxide (WO_3 – SiO_2) catalyst or a phosphoric acid catalyst supported on SiO_2. The phosphoric acid/SiO_2 process is commercially developed in Germany, the Netherland, the United Kingdom, and Japan (Papa, 2011).

$$CH_3CH{=}CH_2 + H_2O \xrightarrow{catalyst} (CH_3)_2CHOH \qquad \text{(eq 1)}$$

Acetone Hydrogenation

Although not a major production method, a few variations exist for the hydrogenation of acetone [$(CH_3)_2C{=}O$] to isopropanol (eq 2). High yields of isopropanol can be achieved through the hydrogenation (reduction using molecular hydrogen (H_2)) of liquid phase acetone over a fixed catalyst bed of Raney-nickel. In addition, hydrogenation of acetone over copper oxide – chromium oxide at 120 °C gives reduced selectivity and conversion relative to the Raney-nickel method. In both cases, it is not essential that the acetone feedstock be of high purity. Aside from these established reactions, advancements in the overall industrial process as well as new catalysts and promoters comprised of chromium, iron, and molybdenum have been reported in the recent patent literature (Bonmann, 2010; Hayes, 2007). Acetone hydrogenation is generally employed when excess acetone is available as a byproduct from another industrial process (Papa, 2011).

$$(CH_3)_2C{=}O + H_2\ \text{(gas)} \xrightarrow{catalyst} (CH_3)_2CHOH \qquad \text{(eq 2)}$$

Fermentation

Isopropanol naturally occurs in the environment as a fermentation and decomposition product of various vegetables and other plants. Not surprisingly, researchers have attempted to harness the fermentative capacities of yeast and bacteria in the production of isopropanol. Some of the more recent advances in this area include the production of mixtures consisting of isopropanol, butanol and ethanol for biofuel applications (Collas, 2012; Lee, 2012). Specifically, the gene encoding the secondary-alcohol dehydrogenase enzyme from *Clostridium beijerinckii*, which catalyzes the reduction of acetone to isopropanol, was cloned into the acetone, butanol and ethanol-producing strain of *Clostridium acetobutylicum* to increase the isopropanol yield. Likewise, synthetic DNA sequences have been successfully inserted into *C. acetobutylicum* to enhance the production of the isopropanol, butanol and ethanol fuel mixture (Dusséaux, 2013). A number of recent patents describing similar technologies are also available (Mochizuki, 2009). In addition, some of the first methods utilizing genetically engineered yeast for the production of isopropanol appeared in the recent patent literature (Muramatsu, 2013a; Muramatsu, 2013b). Notwithstanding these advancements, the body of evidence indicates that fermentative methods using either natural or GM microorganisms are not currently employed in the commercial production of isopropanol.

<u>Evaluation Question #3:</u> Discuss whether the petitioned substance is formulated or manufactured by a chemical process, or created by naturally occurring biological processes (7 U.S.C. § 6502 (21)).

Isopropanol may be considered synthetic or natural (nonsynthetic) depending on the commercial process used for its production. The term "synthetic" is defined by the NOP as "a substance that is formulated or manufactured by a chemical process or by a process that chemically changes a substance extracted from naturally occurring plant, animal, or mineral sources, except that such term shall not apply to substances created by naturally occurring biological processes" (7 CFR 205.2) According to this definition, isopropanol produced through chemical synthesis would be considered a synthetic substance due to the application of synthetic chemicals (reagents and solvents) in both the production as well as the purification/processing of crude isopropanol. Alternatively, isopropanol generated through biological fermentation using naturally derived microorganisms would constitute a nonsynthetic (natural) substance. Commercial isopropanol is produced primarily via direct and indirect hydration of propylene and should therefore be considered a synthetic substance. It is unlikely that residues of chemical precursors/substrates will persist in the final product due to the distillation step and chemical/physical properties of the chemical precursors.

<u>Evaluation Question #4:</u> Describe the persistence or concentration of the petitioned substance and/or its by-products in the environment (7 U.S.C. § 6518 (m) (2)).

This section summarizes technical information related to the persistence of isopropanol in soil, water, and the atmosphere. Although isopropanol is a volatile organic compound and potentially contributes to the formation of ozone and photochemical smog, large-scale releases of isopropanol under the prescribed use pattern in organic livestock production are unlikely. The compiled data indicate that isopropanol is readily biodegradable in soil, water, and air.

Isopropanol may enter the environment as a result of its manufacture in addition to its solvent and chemical intermediate uses. Likewise, isopropanol is naturally emitted as a plant volatile, microbial degradation product of both plant and animal wastes, and biological fermentation product. Larger production sites minimize the release of isopropanol using engineering controls and end-of-pipe abatement systems. Organic wastes from manufacture are also typically incinerated on site or professionally treated using waste contractors. It is anticipated that the largest source of isopropanol released to the environment will result from the use of isopropanol-containing products, such as commercial sanitizers and disinfectants for consumer use, where applications are open and engineering controls are not utilized for the recovery of emitted isopropanol. Isopropanol released to the environment will be predominantly distributed between air and water (HSDB, 2012; UNEP, 1997; EPA, 1995).

If released to soil, isopropanol may be degraded through volatilization and biodegradation processes. Isopropanol is expected to have very high mobility in soils based on its estimated K_{oc} of 1.5. Further, the Henry's Law constant for isopropanol (8.1×10^{-6} atm•m^3/mol) indicates that volatilization from moist soil surfaces is likely to be an important fate process. Isopropanol may also volatilize from dry soil surfaces based on its relatively high vapor pressure. Rapid biodegradation of isopropanol is reported in both aerobic (with oxygen) and anaerobic (without oxygen) conditions; for example, literature studies indicate that the aerobic soil half-life for isopropanol is one to seven days (Howard, 1991). This half-life indicates that, in addition to volatilization, biodegradation is an important environmental fate process for isopropanol in soil (HSDB, 2012; UNEP, 1997).

Volatilization and biodegradation are also primary mechanisms for removal of isopropanol from water. In agreement with the fate of isopropanol in soils described above, isopropanol is not expected to adsorb to suspended solids and sediment based on the K_{oc}. The Henry's Law constant for isopropanol also indicates that isopropanol is likely to rapidly volatilize from water surfaces. Calculated volatilization half-lives for a model river and lake are 86 hours and 29 days, respectively (HSDB, 2012). Rates of aerobic and anaerobic microbial isopropanol biodegradation are rapid enough that isopropanol is not expected to persist for a long duration in ground or surface waters. For example, the aerobic biodegradation of isopropanol in surface water proceeds with half-lives ranging from 26 hours to seven days (Howard, 1991). The estimated Bioconcentration Factor (BCF = 3) suggests that there is low potential for bioaccumulation of isopropanol in aquatic organisms, such as fish (HSDB, 2012). Based on these collective attributes, it has been concluded that isopropanol meets the criteria for being considered readily biodegradable (HSDB, 2012; UNEP, 1997).

If released to the air, isopropanol will exist as a vapor in the atmosphere due to its relatively high vapor pressure (45 mm Hg at 25 ºC). Vapor-phase isopropanol in the atmosphere is subject to oxidation predominantly by photochemically-produced hydroxyl radicals. Half-lives of nine hours to five days have been determined for hydroxyl radical-mediated photodegradation, indicating rapid degradation of isopropanol in both pristine and polluted atmospheres. In contrast, direct photolysis is not expected to be an important transformation process for the degradation of isopropanol. Because isopropanol is highly water soluble, transport from the atmosphere to soil or water surfaces occurs mainly by wet deposition (HSDB, 2012; Alberta, 2004; UNEP, 1997). Isopropanol is a volatile organic compound (VOC) and therefore its industrial emissions are regulated by US EPA to prevent the formation of ozone, a constituent of photochemical smog (US EPA, 2012a).

Evaluation Question #5: Describe the toxicity and mode of action of the substance and of its breakdown products and any contaminants. Describe the persistence and areas of concentration in the environment of the substance and its breakdown products (7 U.S.C. § 6518 (m) (2)).

This section summarizes isopropanol toxicity to five taxa groups, including mammals, freshwater and marine fish, freshwater and marine invertebrates, and terrestrial and aquatic plants. Overall, it can be concluded that isopropanol is slightly toxic to practically non-toxic to most taxa groups evaluated in the literature.

According to US EPA, isopropanol is slightly toxic (Category (III) to practically non-toxic (Category IV) based on acute oral and inhalation toxicity tests as well as primary eye and dermal irritation studies (EPA, 1995). Relatively large LD_{50} and LC_{50} values (i.e., isopropanol doses and air concentrations at which 50 percent mortality of test subjects is observed) were determined, which points to the low toxicity of isopropanol under these exposure routes. Laboratory studies have provided acute oral LD_{50} values of 3,600–4,384 milligrams isopropanol per kilogram body weight (mg/kg) for mice and rats, a dose range consistent with slight toxicity (Category III). Further, acute dermal and inhalation toxicity tests found isopropanol to be practically non-toxic, with a dermal LD_{50} of 12,870 mg/kg and inhalation LC_{50} values of 47–69 mg isopropanol per liter of air (mg/L). In addition to minimal acute toxicity, isopropanol is slightly to moderately (Category III-IV) irritating to the eyes and nonirritating (Category IV) to the skin of rabbits in primary eye and dermal irritation studies. Isopropanol was found to be acutely neurotoxic only at high air concentrations. Specifically, male and female rats exposed to respective isopropanol vapor concentrations of 1,500 and 5,000 parts per million (ppm) exhibited decreased motor activity. Relatively high No Observed Effect Levels of 500 ppm in males and 1,500 ppm in females were determined for this study (US EPA, 1995; US EPA, 2012c).

Repeated exposure toxicity, carcinogenicity, mutagenicity, and reproductive/developmental toxicity were also evaluated for isopropanol in mammals. In subchronic inhalation studies (13 weeks), no treatment-related deaths occurred and only higher concentrations (1,500–5,000 ppm) resulted in reversible motor activity impairment and potential adverse effects on the kidneys. Likewise, no treatment-related mortalities occurred in chronic feeding toxicity studies in which five percent isopropanol was fed to rats in drinking water for 304 days; however, decreased mean body weights, reduced activity, and impaired maze learning ability was observed in isopropanol-treated animals. Carcinogenicity studies in rats exposed to isopropanol vapors at concentrations of 0–5,000 ppm found slight increases in the incidence of granular kidneys, thickened stomachs, and nonneoplastic kidney lesions at higher concentrations. However, the study indicated that none of these findings are of biological significance and no evidence of carcinogenicity was found. Isopropanol is also not genotoxic according to mutagenicity assays (US EPA, 1995; UNEP, 1997).

Reproductive and developmental toxicity studies in which rats or rabbits were treated with isopropanol via oral gavage demonstrated slight to moderate maternal toxicity (NOEL = 240–1,000 mg/kg/day) and only slight developmental toxicity (NOEL = 400–1,200 mg/kg/day). Maternal exposure to elevated vapor concentrations of isopropanol (7,000–10,000 ppm) resulted in an increased number of resorptions (fetal death and in utero absorption) per litter and fetal skeletal malformations (US EPA, 1995). A two-generation reproductive study characterizing the reproductive hazard associated with isopropanol exposure via oral gavage demonstrated a statistically significant decrease in the male mating index of first generation males only. However, the lack of histopathologial findings in the testes of high-dose males and lack of significant effect on the female mating index in either generation suggest that the observed reduction in male mating may not be biologically relevant. The fact that most females became pregnant and no adverse effects on litter size were observed in this study adds further weight to this conclusion (UNEP, 1997).

Studies investigating the toxicity of isopropanol to other terrestrial and aquatic receptors are compiled in the US EPA Ecotox database and summarized in the Ecological Risk Assessment (US EPA, 2013; US EPA, 2012b). Results of 24- and 96-hour acute toxicity screens range from 1,400 to greater than 10,000 mg/L for freshwater and saltwater fish and invertebrates. For example, the relatively high 96-hour LC_{50} of 6,550 mg/L in fathead minnows and 24-hour LC_{50} of >250 mg/L in glass shrimp associated with exposure to isopropanol in tank water indicate that isopropanol is practically non-toxic to freshwater fish and marine invertebrates. Likewise, the 48-hour EC_{50} (effective concentration leading to intoxication in 50 percent of test organisms) of 2,280 mg/L for isopropanol exposure in the freshwater invertebrate, *Daphnia magna*, is consistent with minimal toxicity. The 7-day toxicity threshold concentration of 1,800 mg/L for freshwater algae and EC_{50} value of 2,100 mg/L for lettuce seed germination suggests that the toxicity of isopropanol to terrestrial and aquatic plants is likely to be low. A variety of other microorganisms are also able to tolerate low (≤100 mg/L) concentrations of isopropanol in the environment (UNEP, 1997).

<u>Evaluation Question #6:</u> Describe any environmental contamination that could result from the petitioned substance's manufacture, use, misuse, or disposal (7 U.S.C. § 6518 (m) (3)).

Considering its volatile nature and long-history of production and transportation, releases of isopropanol to the environment are inevitable. Trace quantities of isopropanol have been detected in drinking water samples, while higher air and water concentrations have been observed in industrial areas (HSDB, 2012). Large industrial-scale spills or releases of isopropanol are both infrequent and generally confined. Nevertheless, the release of sufficient quantities of isopropanol to aquatic environments could lead to environmental impairment. Isopropanol has a high biochemical oxygen demand (BOD) and therefore enhanced potential to cause oxygen depletion in aqueous systems (BABEC, 2001). Adverse effects on fish and aquatic plants, ranging from reduced growth rates to outright death, are likely to result from the oxygen depletion accompanying microbial aerobic degradation of large isopropanol volumes in impacted waterways. The toxicity of isopropanol to fish, aquatic invertebrates, and aquatic plants due to oxygen depletion is thus significantly greater than the inherent toxicity of isopropanol to these receptors.

Aside from accidental spills, the risk of environmental contamination from isopropanol released during normal use is minimal. The release of strong acids and bases used in the production of isopropanol due to improper handling/disposal could lead to serious environmental impairments and ecotoxicity in both terrestrial and aquatic environments. However, no incidents involving the release of these chemical feedstocks from isopropanol production facilities have been reported. Further, small amounts of isopropanol are constantly released to the environment as a metabolic product of aerobic microorganisms (e.g., fish spoilage bacteria, beef spoilage bacteria, potato tuber soft rot bacteria), anaerobic microorganisms, fungi (e.g., mushrooms), yeast, and other plants (HSDB, 2012; Alberta, 2004). It is therefore unlikely that large-scale spills and associated environmental contamination would occur under the allowed use of isopropanol as a disinfectant in organic livestock production.

<u>Evaluation Question #7:</u> Describe any known chemical interactions between the petitioned substance and other substances used in organic crop or livestock production or handling. Describe any environmental or human health effects from these chemical interactions (7 U.S.C. § 6518 (m) (1)).

There are no reported chemical interactions between isopropanol and other substances used in organic livestock production. As a solvent, isopropanol may solubilize and thereby enhance the dermal absorption of various chemical residues (e.g., pesticides) deposited on the skin during agricultural production activities. However, technical information regarding this phenomenon was not identified.

In general, isopropanol functions as a disinfectant through the dissolution of lipid membranes and rapid denaturation of proteins. Because proteins are denatured more quickly in the presence of water, enhanced bactericidal activity is generally observed for mixtures of isopropanol and water when compared to concentrated isopropanol, which functions as a strong dehydrating agent (CDC, 2008; McDonnell, 1999). This crude observation provides qualitative support for the proposed mechanism, which relies heavily upon the ability of isopropanol to denature proteins. Isopropanol is able to effectively destroy many types of bacterial and viral cells due to this mode of action; however, it is ineffective against bacterial spores because the substance evaporates before it can effective penetrate the membrane and lead to protein denaturation (CDC, 2008).

<u>Evaluation Question #8:</u> Describe any effects of the petitioned substance on biological or chemical interactions in the agro-ecosystem, including physiological effects on soil organisms (including the salt index and solubility of the soil), crops, and livestock (7 U.S.C. § 6518 (m) (5)).

The current technical evaluation concerns the use of isopropanol as a disinfectant for livestock housing, surfaces and production implements as well as a topical antiseptic during medical treatments in organic livestock production. When used for these purposes, it is unlikely that isopropanol will regularly interact with components of the terrestrial agro-ecosystem (i.e., agricultural land). Further, technical information regarding non-target wildlife toxicity resulting from the use of disinfectant products containing isopropanol in livestock production is lacking. Any potential leakage of isopropanol, particularly large-scale spills, near the agro-ecosystem would be neither routine nor widespread.

Toxicity toward soil-dwelling organisms may result from the use and manufacture of isopropanol. Although limited information is available on the toxicity of isopropanol on soil bacteria, it has been determined that certain bacterial strains, including *Bacillus*, can tolerate and therefore be used for the biodegradation of dilute isopropanol solutions (Ruiz, 2004; Al-Awadhi, 1990). In contrast, the scientific literature is replete with information regarding the ability of more concentrated isopropanol solutions (approximately 70 percent in water) to kill the bacterial pathogens *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Escherichia coli* (Bradford, 2013; Rushdy, 2011), among other bacterial and viral microorganisms (CDC, 2008; US EPA, 1995). Concentrated isopropanol solutions are therefore likely to kill beneficial soil bacteria and small invertebrates, such as earthworms.

Plants generally tend to have a high tolerance for isopropanol (Alberta, 2004). Complete inhibition of barley grain germination required four days of exposure to high concentrations of isopropanol (39,420 mg isopropanol/L water). A related study noted that white amaranth seeds were unaffected after five hours of incubation on filter papers saturated with a concentrated (36,000 mg/L) isopropanol solution. For lettuce, an isopropanol concentration of 2,100 mg/L inhibited germination by 50 percent, while complete inhibition was achieved at 6,000 mg/L. Intriguingly, lettuce germination was reconstituted at significantly elevated isopropanol concentrations (≥18,000 mg/L), reaching a maximum of 62 percent at 26,000 mg/L. Cellular assays of soybean root sections revealed delayed onset of growth for one and two weeks at respective isopropanol concentrations of 10,000 and 20,000 mg/L (Alberta, 2004). It is highly unlikely that the relatively small volume, controlled applications of isopropanol in livestock production would lead to major spills and concomitant adverse effects on the agro-ecosystem.

Accidental release of chemical reagents during the production process may also lead to ecological impairment. Strong acids (e.g., sulfuric acid) and bases (e.g., potassium hydroxide) are used in the chemical synthesis and, to a lesser extent, the fermentative preparation of isopropanol. Improper use or disposal of acidic and basic reagents during the production of isopropanol could affect both the pH and chemical composition of the soil, potentially resulting in physiological effects on soil organisms. Likewise, improper treatment and subsequent release of synthetic wastes and fermentation broths could impair soil populations. These types of spill scenarios are unlikely due to manufacturing safeguards.

Large scale releases of isopropanol-based disinfectants near rivers, ponds and lakes could lead to population level impacts due to oxygen depletion and subsequent fish kills. Otherwise, technical information regarding the potential impacts of isopropanol on endangered species, populations, viability or reproduction of non-target organisms and the potential for measurable reductions in genetic, species or ecosystem biodiversity, is lacking.

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

Isopropanol is not expected to be persistent or hazardous to the environment under the prescribed use pattern as a disinfectant in organic livestock production (US EPA, 2012a; USDB, 2012; Alberta, 2004; UNEP, 1997; US EPA, 1995). Isopropanol generally partitions between the atmosphere and water. It is readily biodegradable and is not expected to accumulate in soils, plant material or animal tissues. In the air, isopropanol is expected to undergo rapid photodegradation in the presence of photochemically-derived hydroxyl radicals. Isopropanol also has a relatively low potential to generate ground level ozone and photochemical smog compared to other VOCs. Although unlikely, large spills of isopropanol from manufacturing sites and transportation vessels could lead to ecological impairment due to oxygen depletion in impacted waterways. Spills of chemical feedstocks used in the production of isopropanol, such as strong acids and bases, could adversely affect terrestrial and aquatic systems; however, specific occurrences have not been documented and are unlikely due to modern manufacturing safeguards.

According to US EPA and World Health Organization (WHO) literature reviews, isopropanol is practically non-toxic to slightly toxic to most biological receptors (US EPA, 2012b; Alberta, 2004; UNEP, 1997; US EPA, 1995). For mammals, isopropanol is slightly toxic to non-toxic (Category III-IV) based on acute oral and inhalation toxicity tests, slightly/moderately irritating to the eyes, and nonirritating to the skin. In addition, *in vitro* and *in vivo* animal studies have demonstrated that isopropanol is neither mutagenic nor carcinogenic. Laboratory rodents exposed to excessively high doses of isopropanol over extended time periods exhibited narcosis; however, none of the observed adverse effects to the nervous system were irreversible. Minimal toxicity has been noted in studies evaluating the germination and growth efficiency of seeds and plants exposed to high concentrations of isopropanol. Although isopropanol is not particularly toxic to aquatic organisms, such as fish, aquatic invertebrates and aquatic plants, oxygen depletion due to large isopropanol spills could lead to population-level toxicity and death for these receptors. It is unlikely that the proposed use pattern of isopropanol in organic livestock production would lead to significant isopropanol exposure in the agro-ecosystem.

No incidents of eutrophication have been associated with the use, manufacture, or environmental release of isopropanol. In contrast, intensive corn farming for the production of fuel ethanol has led to water quality impairment near agricultural areas due to the incidental discharge of nitrogen and phosphorous fertilizers near waterways (UCS, 2011; Kim, 2008). The apparent lack of similar eutrophication incidents linked to isopropanol likely stems from the fact that industrial isopropanol is generated through chemical synthesis rather than the fermentation of agricultural feedstocks such as cornstarch.

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

A high production volume chemical, isopropanol is widely used as an industrial solvent and as an ingredient in numerous industrial and consumer products. As such, the potential exists for widespread exposure of workers and consumers to isopropanol (Kawai, 1990).

In general, isopropanol is characterized as slightly to not acutely toxic to humans by the oral, dermal and inhalation routes of exposure (US EPA, 2012c; Alberta, 2004; UNEP, 1997; US EPA, 1995). This observation is not surprising considering the ubiquitous nature of isopropanol in hygiene products, fragrances, cosmetics, adhesives, and other consumer products. Human volunteers exposed to 400 ppm isopropanol vapors for 3–5 minutes reported mild irritation to the eyes, nose and throat. In addition, isopropanol produced little irritation when tested on the skin of human volunteers. Incidents of isopropanol poisoning in humans have resulted from the intentional ingestion of isopropanol, particularly among alcoholics or suicidal individuals. In these cases, pulmonary difficulty, nausea, vomiting, headache, and varying degrees of central nervous system depression are typical (UNEP, 1997). The vast majority of animal studies are conducted orally at excessively high doses of isopropanol to determine the dose-response relationship. Although not entirely relevant to the evaluation of isopropanol toxicity from exposure to disinfectants, these studies support the conclusion that isopropanol is slightly to practically non-toxic to humans at moderate to low doses. See Evaluation Question #5 for additional information regarding isopropanol toxicity studies conducted in laboratory mammals.

Isopropanol has also been evaluated for mutagenic and carcinogenic activity. Isopropanol tested negative in bacterial mutation assays with and without metabolic activation using exogenous mammalian cells. Mitotic aberrations in rat bone marrow cells were observed in a four-month vapor exposure study; however, the results of this study are questionable since the authors did not report the number of rats exposed, their sex, or strain. In contrast, isopropanol did not induce cancerous micronuclei formation in the bone marrow of mice in an *in vivo* study involving injections of isopropanol into the body cavities of mice at elevated doses (350–2,500 mg/kg body weight). Isopropanol also produced negative results in chromatid exchange tests and fungal assays for aneuploidy (a form of chromosomal aberration). There is little evidence to suggest that isopropanol is genotoxic in animals and humans (Alberta, 2004).

Occupational epidemiological studies have been conducted on workers involved in either the manufacturing or use of isopropanol. A number of retrospective cohort studies have reported an increased incidence of respiratory tract cancers (paranasal sinuses, larynx, and lungs) in workers at factories where isopropanol was manufactured using the strong-acid process (IARC, 1999). However, concomitant exposure to diisopropyl sulfate, an intermediate in this process, as well as isopropyl oils and sulfuric acid mists may also lead to the observed carcinogenic effects and represent confounding factors in these studies (IARC, 1999; Alberta, 2004). The studies also failed to quantify isopropanol exposure levels and control for smoking rates among workers (Alberta, 2004). Collectively, these confounding factors greatly limit the weight of these studies. In small case-control studies of workers in a chemical plant and rubber plant, there is no evidence of an association between exposure to isopropanol and the incidence of gliomas or lymphocytic leukemia (Alberta, 2004).

The International Agency for Research on Cancer (IARC) concluded that there is inadequate evidence for the carcinogenicity of isopropanol in humans and experimental animals following review of available studies on the carcinogenicity, genotoxicity and mutagenicity of isopropanol. As such, IARC determined that "isopropanol is not classifiable as to its carcinogenicity to humans (Group 3)" (IARC, 1999; IARC, 2013). US EPA and Health Canada have not classified isopropanol according to its carcinogenicity status. In contrast, diisopropyl sulfate is listed as a California Proposition 65 carcinogen and strong inorganic acid mists containing sulfuric acid is listed as a Proposition 65 and IARC Group 1 carcinogen (CA EPA, 2013; IARC, 2013).

Evaluation Question #11: Describe all natural (non-synthetic) substances or products which may be used in place of a petitioned substance (7 U.S.C. § 6517 (c) (1) (A) (ii)). Provide a list of allowed substances that may be used in place of the petitioned substance (7 U.S.C. § 6518 (m) (6)).

Technical information regarding the efficacy of natural, nonsynthetic agricultural commodities or products that could substitute for isopropanol as a disinfectant in organic livestock production is limited. Natural (nonsynthetic) sources of ethanol and organic acids (e.g., acetic acid, citric acid and lactic acid) may be used for disinfection. Certain essential oils also exhibit antiviral and antibacterial properties, and are commonly used in homemade hand sanitizers. Examples of the strongest and most commonly used antiseptic essential oils include clove oil, melaleuca oil, and oregano oil. In addition, pine oil, basil oil, cinnamon oil, eucalyptus oil, helichrysum oil, lemon and lime oils, peppermint oil, tea tree oil, and thyme oil are also used as antiseptic substances. Aloe vera contains six antispectic agents (lupeol, salicylic acid, urea nitrogen cinnamonic acid, phenols and sulfur) with inhibitory action on fungi, bacteria and viruses (Surjushe, 2008). Depending on the required potency and intended application, essential oils may be used in pure form or as a mixture in carrier, such as water. University agricultural extension publication repositories contained no articles related to the practice of using essential oils as disinfectants or any performance data for these oils relative to isopropanol. It is therefore uncertain whether essential oil mixtures could serve as viable, naturally derived alternatives to isopropanol-based products for equipment/surface disinfection and animal skin antisepsis in livestock production.

A wide variety of synthetic substances are available for sanitizing and disinfecting livestock housing and production equipment, and for topical antisepsis during medical treatments. Acids (acetic acid), alcohols (ethanol and isopropanol), aldehydes (formaldehyde and glutaraldehyde), alkalis (sodium or ammonium hydroxide, sodium carbonate, calcium oxide), Biguanides (chlorhexidine), chlorine compounds (sodium hypochlorite), iodine compounds and complexes (iodophors), oxidizing agents (hydrogen peroxide and peracetic acid), phenols, and quaternary ammonium compounds are commonly used as part of disinfection regimens in veterinary and animal housing environments (Dvorak, 2008). In addition, many of these chemical disinfectants are used as disinfectant solutions in footbaths (i.e., boot-washing stations) and for the disinfection of equipment and other surfaces. Not all of these substances, however, are allowed for use in organic livestock production. The USDA recommends sodium hypochlorite, acetic acid, sodium carbonate, and/or sodium hydroxide for controlling foot-and-mouth disease outbreaks (USDA, 2005). Additionally, hypochlorite or other suitable disinfectants are commonly used on automatic feeding machines and sodium hydroxide is used against classic swine fever in Chile (Fotheringham, 1995). Hydrogen peroxide is also a widely used topical antiseptic in medical operations. Utilizing a combination of disinfection chemistries is not only advantageous for addressing various situations (i.e., target pest, surface, etc.), but also necessary for preventing microbial resistance (Dvorak, 2008; USDA, 2005).

In addition to isopropanol (7 CFR 205.603(a)(1)(ii)), the National List of Allowed and Prohibited Substances permits the use of the following synthetic materials as disinfectants, sanitizers, and medical treatments in organic livestock production:

- **Ethanol** (CH_3CH_2OH) 7 CFR 205.603(a)(1)(i)
- **Chlorhexidine** 7 CFR 205.603(a)(6)
  - Allowed for surgical procedures conducted by a veterinarian. Allowed for use as a teat dip when alternative germicidal agents and/or physical barriers have lost their effectiveness.
- **Chlorine Materials**
  - Allowed for disinfecting and sanitizing facilities and equipment.
    - **Calcium hypochlorite** ($Ca(ClO)_2$) 7 CFR 205.603(a)(7)(i)
    - **Chlorine dioxide** (ClO_2) 7 CFR 205.603(a)(7)(ii)
    - **Sodium hypochlorite** (NaClO) 7 CFR 205.603(a)(7)(iii)
- **Hydrogen peroxide** (H_2O_2) 7 CFR 205.603(a)(13)
- **Iodine** 7 CFR 205.603(a)(14)
- **Peroxyacetic acid/peracetic acid** 7 CFR 205.603(a)(19)
  - Allowed for sanitizing facility and processing equipment.
- **Phosphoric acid** (H_3PO_4) 7 CFR 205.603(a)(20)
  - Allowed as an equipment cleanser, provided the substance does not directly contact organically managed livestock or land.

<u>Evaluation Question #12:</u> Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

Sterilization methods are critical for preventing the spread of deleterious bacterial, fungal and viral pathogens on production surfaces (i.e., livestock housing and equipment) and animal skin. In addition to chemical disinfectants, heat, light and radiation may also be used to reduce or eliminate microorganisms in livestock housing environments (Dvorak, 2008). Heat is one of the most established physical controls against deleterious microorganisms and is a fairly reliable sterilization method. Moist heat is most effective (e.g., steam) and requires less time, but dry heat (e.g., flame or baking) may also be used for inactivating microorganisms. Ultraviolet light is also capable of inactivating viruses, bacteria and fungi, but is limited by its lack of surface penetration. Less frequently used forms of radiation include microwaves and gamma radiation. Although thermal treatments may be effective for disinfecting certain pieces of equipment, other strategies would be required for eliminating microbes from animal housing surfaces and animal skin. Frequently changing the animal's bedding and/or using inorganic bedding (i.e., sand) may also reduce bacteria levels in livestock housing (Dvorak, 2008; Fotheringham, 1995). Likewise, removing debris from the production areas and ensuring the cleanliness of equipment are important steps for minimizing microorganism populations on and around livestock.

Microbial control regimens that exclude chemical disinfection are generally not advised, particularly for pathogens potentially present on animal skins and equipment surfaces. Although alternative practices are not available, a variety of alternative substances are presented in Evaluation Question #11.

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