Iodine
Livestock

Identification of Petitioned Substance

Chemical Names:
Iodine

Other Name:
Iodophor

Trade Names:
CAS Numbers:
FS-102 Sanitizer & Udderwash
Udder-San Sanitizer and Udderwash

7553-56-2 (Iodine)
11096-42-7 (Nonylphenoxypolyethoxyethanol–iodine complex)

Other Codes:
231-442-4 (EINECS, Iodine)

Summary of Petitioned Use

The National Organic Program (NOP) final rule currently allows the use of iodine in organic livestock production under 7 CFR §205.603(a)(14) as a disinfectant, sanitizer and medical treatment, as well as 7 CFR §205.603(b)(3) for use as a topical treatment (i.e., teat cleanser for milk producing animals). In this report, updated and targeted technical information is compiled to augment the 1994 Technical Advisory Panel (TAP) Report on iodine in support of the National Organic Standard's Board's sunset review of iodine teat dips in organic livestock production.

Characterization of Petitioned Substance

Composition of the Substance:

A variety of substances containing iodine are used for antisepsis and disinfection. The observed activity of these commercial disinfectants is based on the antimicrobial properties of molecular iodine (I_2), which consists of two covalently bonded atoms of elemental iodine (I). For industrial uses, I_2 is commonly mixed with surface-active agents (surfactants) to enhance the water solubility of I_2 and also to sequester the available I_2 for extended release in disinfectant products. Generally referred to as iodophors, these "complexes" consist of up to 20% I_2 by weight in loose combination with nonionic surfactants such as nonylphenol polyethylene glycol ether (Lauterbach & Uber, 2011). Likewise, acidic species are also used to solubilize small amounts of I_2 in water. Addition information regarding the production of soluble iodine complexes is provided in "source or origin of the substance" and Evaluation Question #2. See Figure 1 below for the molecular structure of iodine (I_2) and an example surfactant complex with I_2.

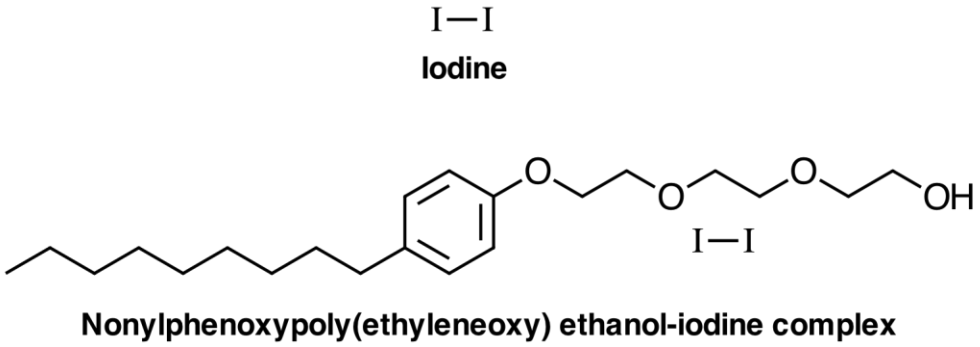

Figure 1. Molecular iodine (I_2) used in disinfectants is commonly formulated with nonionic surfactants to generate iodophors.

Source or Origin of the Substance:

Molecular iodine (I_2) production processes generally utilize raw materials containing iodine, including seaweeds, mineral deposits, and oil well or natural gas brines. Early production processes involved the drying and burning of seaweeds followed by chemical extraction of iodides and oxidation of these iodides to free iodine (I_2). Large amounts of iodine are commercially generated through the reaction of iodate and iodide solutions obtained as by-products of nitrate ore processing in Chile. Most other producers use naturally occurring brine from oil and gas fields as sources of iodine. In general, these industrial methods involve purification of the iodide containing brines with sulfuric acid (H_2SO_4) followed by oxidation of iodide (I^-) to iodine (I_2) using chlorine (Cl_2) gas and extraction of iodine from brine solutions in a countercurrent air blowout process. Iodine used in disinfectant products is generally formulated with nonionic surfactants such as nonylphenol polyethylene glycol ethers (Figure 1). See Evaluation Question #2 for details regarding the reaction conditions utilized in commercial production methods.

Properties of the Substance:

Molecular iodine (I_2) exists as a blue/black lustrous solid as well as a violet gas with a sharp, characteristic odor. The chemical and physical properties of I_2 are provided below in Table 2, and their respective impacts on the environmental fate of I_2 are discussed in Evaluation Question #4.

Table 1. Physical and Chemical Properties of Iodine

Property	Value/Description
Color	Bluish-black (solid); violet (gas)
Physical State	Lustrous solid; scales or plates
Molecular Formula	I_2
Molecular Weight, g/mol	253.8
Freezing Point, °C	113.7
Boiling Point, °C	184.4
Density, g/mL	4.93 (solid, 20 °C); 6.75 (gas; 180 °C)
Solubility in water at 20 °C, g/L	0.03–0.33 (virtually insoluble to poorly soluble)
Solubility in organic solvents	Miscible in many organic solvents, including chloroform, cyclohexane, and alcohols (methanol and ethanol)
Corrosivity	Vapor is corrosive
Hydrolysis	I_2 dissolved in water hydrolyzes slightly to form a mixture of hypoiodous acid (HIO), iodide (I^-) and free acid (H_3O^+); $K_{eq} = 5.4 \times 10^{-13}$ at 25 °C.
Photoreactivity	I_2 and organic iodides (e.g., methyl iodide) undergo photochemical reactions to form iodine radicals, which form other iodine species through various reaction pathways.
Octanol/Water Partition Coefficient (K_{ow})	309
Vapor Pressure at 25 °C, mm Hg	0.23–0.31
Henry's Law Constant, atm•m^3/mol	0.32

Data Sources: HSDB, 2006; US EPA, 2006; Lauterbach & Uber, 2011; ATSDR, 2004; Sander, 1999.

Specific Uses of the Substance:

Organic and conventional dairy operators commonly apply iodine teat dips both before and after milking. Iodine is currently allowed on the National List as an antimicrobial treatment for the prevention and control of mastitis in milk producing animals (7 CFR 205.603(b)(3)) caused by contagious pathogens such as *Staphylococcus aureus*, *Streptococcus agalactiae* and *Mycoplasma spp* (USDA, 2003).

Experts in the field have concluded that post-milking teat antisepsis with a germicidal solution is the single most effective practice for mastitis prevention (Nickerson, 2011). Even under the most hygienic conditions, the transfer of bacteria and other microorganisms during milking is inevitable. It is therefore highly recommended that operators disinfect teats with an appropriate microbiocide (teat dip or spray) as soon as possible after the milking apparatus is removed (Nickerson, 2001). Developed more recently, the pre-milking teat dip method served as a replacement for udder washing to reduce the coliform bacteria load on

teat skin followed by drying with paper towels (Nickerson, 2001). Pre-dipping effectively reduces the spread of microorganisms and associated incidence of mastitis in dairy herds, and minimizes the number of bacteria entering raw milk (Nickerson, 2011). It was found that the pre-dipping method was more effective than udder washing for killing bacteria, but skin irritation was observed at higher iodine concentrations. In addition, iodine residues were detected in the milk of treated animals. Lowering iodine concentrations from 1% to 0.1–0.5% in pre-milking teat dips prevented skin irritation and reduced iodine residues in milk without compromising efficacy. In fact, these lower concentrations still resulted in 50 to 80% reduction in the rate of new mastitis infections relative to untreated cows (Nickerson, 2001). Smaller dairy operations typically perform teat dips manually using disinfectant dip cups, while mechanical systems involving a combination of rotating brushes with disinfecting solutions (e.g., iodophors) have also proven advantageous for large-scale milk producers (Dole, 2012; Eriksson, 2003).

In addition to teat dips, iodine is also used for disinfection in agricultural, medical, food processing and a variety of other settings. Iodine is allowed for use on the National List as a disinfectant, sanitizer and medical treatment, as applicable, in organic livestock production (7 CFR 205.603(a)(14)). For example, iodine may be used to disinfect surfaces, teat cup liners and other components of the milking apparatus as part of a backflush system between milking events (VCE, 2001; Hogan, 1984). Iodine solutions can also be used to disinfect food and water dishes for control of infectious disease outbreaks on agricultural premises (USDA, 2005).

Numerous iodine containing substances are also used as antiseptics for skin wounds, as disinfecting agents in hospitals and laboratories, and for the emergency disinfection of drinking water in the field (WHO, 2003). Health professionals have long used tinctures of iodine as antiseptics, and iodophors have been used for both antisepsis and surface disinfection. For example, the poly(vinyl pyrrolidinone)–iodine complex (PVP–iodine) containing about ten percent available iodine has been used extensively in hospitals and elsewhere because of its germicidal, bactericidal, fungicidal and general disinfecting properties (Lauterbach & Uber, 2011). Other iodophor uses include the disinfection of blood culture bottles and medical equipment, such as thermometers and endoscopes (CDC, 2008). Because iodophors formulated as antiseptics contain less free iodine than those formulated as disinfectants, antiseptic iodophors are not suitable for hard-surface disinfection (CDC, 2008). More concentrated iodophors may also be used to disinfect the surfaces of food-processing plants and for sanitation of dishes in restaurants (Lauterbach & Uber, 2011). The ability of iodine to effectively disinfect water against bacteria, viruses and cysts led to the development of iodine tablets, such as tetraglycine hydroperiodide, that release small amounts of molecular iodine for emergency water disinfection (US EPA, 2006; Lauterbach & Uber, 2011).

Beyond the disinfectant applications, iodine and iodine compounds are used as drugs, organic synthetic intermediates in chemical and pharmaceutical research and development, photographic development materials, and in X-ray contrast media. Drugs containing iodine have been classified as antiseptic, antispasmodic, coronary vasodilators, diagnostic, endocrine active, and neuro-muscular blocking agents, in addition to many other medical classifications. Organic (non-ionic) and ionic iodine (i.e., iodide) have been successfully employed as X-ray contrast media to improve the visibility of internal bodily structures in X-ray based imaging technologies. Likewise, ionic silver compounds such as silver iodide have been used for the development of film; however, this use pattern has decreased with improvements in digital imaging (Lauterbach & Uber, 2011).

Approved Legal Uses of the Substance:

Molecular iodine, iodophor complexes, and other iodine compounds are permitted for a wide variety of applications, ranging from surface disinfection to direct and indirect food uses. Legal uses of iodine according to US Environmental Protection Agency (US EPA) and US Food and Drug Administration (FDA) rules are summarized in the following paragraphs.

US Environmental Protection Agency

Iodine and iodophor complexes are used for a variety of indoor antimicrobial uses. In these capacities, iodine compounds function as microbiocides by releasing molecular iodine (I_2). Products containing iodine as the active ingredient were initially registered in the US Department of Agriculture (USDA) in 1948 (US EPA, 2006). Uses of iodine and iodophors that are currently registered by US EPA include, but are not

limited to, emergency drinking water purification, fresh food sanitization (potassium iodide), food-contact surface sanitization, hospital surface disinfection, materials preservation, and addition to commercial and industrial water-cooling tower systems. There were 51 EPA-registered products containing iodine or an iodophor active ingredient as of October 2014 (US EPA, 2014). In 2006, approximately two million pounds of iodine and iodophor complexes were incorporated into commercially available antimicrobial products (US EPA, 2006a). Additionally, US EPA exempted iodophor complexes from the requirement of a tolerance when used as sanitizers in poultry drinking water (40 CFR 180.1022):

> *The aqueous solution of hydroiodic acid and elemental iodine, including one or both of the surfactants (a) polyoxypropylene-polyoxyethylene glycol nonionic block polymers (minimum average molecular weight 1,900) and (b) α-(p-nonylphenyl)-omega-hydroxypoly (oxyethylene) having a maximum average molecular weight of 748 and in which the nonyl group is a propylene trimer isomer, is exempted from the requirement of a tolerance for residues in egg, and poultry, rate; poultry, meat; poultry, meat byproducts when used as a sanitizer in poultry drinking water.*

Other tolerance exemptions for residues of iodine and iodophor complexes are established under 40 CFR 180.940. The ten tolerance exemptions that exist for iodine and iodophor complexes when used as ingredients in antimicrobial pesticide formulations include listings for molecular iodine, potassium iodide, sodium iodide and hydriodic acid. Residues of molecular iodine are exempted from the requirement of a tolerance when antimicrobial products are used on semi-permanent or permanent food-contact surfaces with adequate draining before contact with food. Iodine disinfectants may be applied to food-contact surfaces in public eating-places, dairy-processing equipment, and food-processing equipment and utensils. According to 40 CFR 180.940(a)(b)(c), "when ready for use, the total end-use concentration of all iodide-producing chemicals in the solution is not to exceed 25 ppm of titratable iodine" (US EPA, 2006b).

US Food and Drug Administration

The FDA has approved numerous legal uses of molecular iodine and related compounds may be used in food surface disinfection, as supplements in food and in certain drugs. A variety of aqueous solutions containing iodine, including iodophors, are permitted indirect food additives as "substances utilized to control the growth of microorganisms" (21 CFR 178.1010). According to this rule, the listed substances may be safely used on food-processing equipment and utensils, and on other food-contact articles as specified in the subsections of the rule. As an example, FDA allows the following use pattern for a subset of iodine complexes:

> *An aqueous solution containing elemental iodine, butoxy monoether of mixed (ethylene-propylene) polyalkylene glycol having a minimum average molecular weight of 2,400 and [alpha]-lauroyl-omega-hydroxypoly (oxyethylene) with an average 8–9 moles of ethylene oxide and an average molecular weight of 400. In addition to use on food-processing equipment and utensils, this solution may be used on beverage containers, including milk containers or equipment.*

According to 21 CFR 333.210, the iodophor complex povidone-iodine (10%), is an allowed topical antimicrobial drug product for over-the-counter human use. Related iodine salts, including calcium iodate, cuprous iodide, potassium iodate and potassium iodide and potassium iodate are direct food substances affirmed as generally recognized as safe (GRAS) (21 CFR 184). Calcium iodate, calcium iodobehenate, cuprous iodide, 3,5-diiodosalicylic acid, ethylenediamine dihydroiodide, potassium iodate, potassium iodide, sodium iodate, sodium iodide and thymol iodide are iodine containing substances that are considered GRAS when added to animal feeds as nutritional dietary supplements at levels consistent with good feeding practice (21 CFR 582.80). Further, potassium iodide is permitted for direct addition to food for human consumption "as a source of the essential mineral iodine" (21 DFR 172.375). FDA rules also indicate that infant formula should contain the nutrient iodine at levels between five and 75 micrograms per 100 kilocalories of formula (21 CFR 107.100).

Although iodophor products are FDA approved for food surface disinfection, iodine-based teat dips are considered unapproved animal drugs according to FDA regulations. The FDA published a proposed regulation in the Federal Register of 1977 (42 FR 40217) which would designate teat dips as new animal drugs and require the evaluation of marketed teat dip products for safety and efficacy under the New Animal Drug Application (NADA) approval process (FDA, 2014). However, the proposed regulation has

not been finalized. Teat dips and udder washes classified as animal drugs may currently be marketed for mastitis control and prevention without NADA approval. As a result, the labels of iodophor teat dip products—such as ICON 10000 X Iodine Teat Dip Concentrate formulated with the nonylphenol ethoxylate iodine complex—typically indicate that FDA has not found the drug to be safe and effective and therefore has not approved the product labeling (IBA Inc, 2014). According to the FDA Grade "A" Pasteurized Milk Ordinance, "udders and teats of all milking animals are clean and dry before milking. Teats shall be cleaned, treated with a sanitizing solution and dry just prior to milking" (FDA, 2011).

Action of the Substance:

Data from product manufacturers have demonstrated that commercial iodophors are bactericidal, virucidal, fungicidal and tuberculocidal at their recommended dilution rate, but are less efficacious against bacterial spores (CDC, 2008). In general, the oxidizing agents iodine, chlorine, chlorine dioxide, ozone and bromine annihilate pathogenic organisms by irreversibly destroying cells and disrupting metabolic processes, such as biosynthesis and development (Punyani, 2006). The antimicrobial mode of action of iodophor complexes is related to the ability of molecular iodine (I_2) to penetrate the cell wall of microorganisms quickly and disrupt the structure and synthesis of proteins and nucleic acids (CDC, 2008). Specifically, iodine targets the free-sulfur amino acids cysteine and methionine, nucleotides and fatty acids, which ultimately results in cell death (McDonnell & Russell, 1999). In addition, iodine interferes with the transport of electrons through electrophilic additions with the enzymes of the respiratory chain in microorganisms (Maris, 1995). Less is known about the antiviral action of iodine, but nonlipid viruses and parvoviruses are less sensitive than lipid-enveloped viruses (McDonnell & Russell, 1999).

Antimicrobial resistance is a significant concern due to the frequent use of iodine-based teat dips for mastitis prevention. In one study, *Staphylococcus aureus* resistance was readily induced *in vitro* through the repeated treatment of bacterial isolates with sub-lethal concentrations of a nonylphenol ethoxylate iodophor product (Behiry, 2012). The authors found no evidence of cross-resistance to antibiotics such as streptomycin and tetracycline in *S. aureus* strains that had adapted to iodophor. In contrast, a separate study demonstrated no diminution in the susceptibility of eight strains of *S. aureus* repeatedly (15 times) exposed to sub-lethal concentrations of a commercial iodophor (Hogan & Smith, 1989). It has been concluded that the "scientific evidence does not support a widespread emerging resistance among mastitis pathogens to antimicrobial drugs" (Pritchard, 2006); however, researchers caution that resistance of pathogens such as *S. aureus* to chemical disinfectants may develop if these compounds are used at concentrations below those required for optimal antimicrobial effects (Behiry, 2012). The work of Azizoglu *et al.* (2013) indicates that the free iodine concentrations (≥ 0.1%) in formulated iodophor products are effective in eliminating the *S. aureus* in liquid media.

Because iodine reacts with organic matter in the process of disinfection, it is likely that the contamination of commercial iodophors with manure, soil, milk or other organic substances would inactivate the available iodine in the antimicrobial solution. Contamination with manure and soil would therefore diminish the efficacy of iodine teat dips. For this reason, mastitis specialists recommend that operators wash teats to remove manure and dirt prior to applying germicidal teat treatments (Nickerson, 2001). Likewise, the labels of udder disinfection products commonly direct applicators to "discard udder washing solution when the color fades noticeably or when it becomes visibly dirty" (Webco, 2006).

Combinations of the Substance:

Various chemical substances are added in the production of commercially available teat dip products. Many of the iodophors commonly used for disinfection in the dairy industry consist of iodine mixed with polymeric nonionic surfactants, such as the polyalkylene glycol and polyvinylpyrrolidone carriers. The nonylphenol ethoxylates (NPEs), polyoxyethylene nonylphenol (CAS# 9016-45-9) and ethoxylated p-nonylphenol (CAS# 26027-38-3), as well as polyvinylpyrrolidone (CAS# 9003-39-8) and other potential polymeric carriers are US EPA List 4 Inerts (US EPA, 2004a) when used in pesticides, including antimicrobial sanitizers. When used in animal drugs (e.g. teat dips), these substances are considered excipients, and are subject to restrictions at section 205.603(f). This rule states that a given excipient may be used in the manufacture of drugs used to treat organic livestock when the excipient is: (1) identified as GRAS by FDA, (2) approved by FDA as a food additive, or (3) included in the FDA review and approval of a New Animal Drug Application or New Drug Application. For example, polyvinylpyrrolidone (CAS#

9003-39-8) is included on FDA's list of Everything Added to Food in the United States and thus may be used in the manufacture of iodine-based teat dips for organic livestock (FDA, 2013b).

Manufacturers commonly incorporate conditioners into iodine teat dip products to replace the protective oils that polymeric surfactants (i.e., detergents) used as complexing agents remove from animal skin during treatment. Moisturizers such as glycerin and propylene are normally added at concentrations ranging from two to ten percent of the product formulation (Universal, 2011; Nickerson, 2001). Further, glycerin produced through the hydrolysis of fats or oils is allowed as a livestock teat dip on the National List (7 CFR 205.603(a)(12)). Lanolin may also be added to iodophor teat dip products as an emollient to replace natural oils lost from the affected skin of dairy cows (Nickerson, 2011).

Status

Historic Use:

In 1994, the National Organic Standards Board recommended that iodine be included on the National List as an allowed synthetic substance for use in bovine teat dips (USDA, 1994). It was discovered in 1958 that dipping teats in 0.1, 1 and 2.5% acidic iodine solutions significantly reduced the numbers of *Staphylococci* that were recovered from milking machine liners (Boddie, 2000). This observation prompted teat dip manufacturers to incorporate iodine into commercially available teat dip products. Based on this report and the original patent literature, it can be concluded that iodophor teat dips have been used in conventional dairy operations since the late 1950s or early 1960s.

Organic Foods Production Act, USDA Final Rule:

The National Organic Program (NOP) final rule currently allows the use of iodine as a disinfectant, sanitizer and medical treatment in organic livestock production under 7 CFR 205.603(a)(14). In addition, iodine is an allowed topical treatment and external parasiticide (i.e., teat dip) according to 7 CFR 205.603(b)(3). This report was prepared for the National Organic Standards Board's sunset review of iodine as an approved synthetic teat dip substance.

International

Several international organizations have provided guidance on the application of synthetic iodine agents in organic livestock production. Among these are regulatory agencies (EU, Canada, Japan) and independent organic standards organizations (IFOAM). International regulations and standards are described in the following sub-sections.

Canadian General Standards Board

Although iodine and teat dipping practices are not described in the General Principles and Management Standards, iodine is included on the Canadian Permitted Substances List for Livestock Production (CAN, 2011a; CAN, 2011b). Specifically, section 5.3 permits the use of iodine as a topical disinfectant:

> *For use as a topical disinfectant. Sources include potassium iodide and elemental iodine. As a cleaning agent, shall be followed by a hot-water rinse. Non-elemental only; not to exceed 5% solution by volume (e.g., iodophors).*

Iodine is also included in section 7.4 of the Canadian Permitted Substances List for Cleaners, Disinfectants and Sanitizers allowed on food contact surfaces including equipment, provided that substances are removed from food contact surfaces prior to organic production (CAN, 2011b).

European Union

According to Article 23 (4) of the Commission Regulation concerning organic production and labeling of organic products,

> *Housing, pens, equipment and utensils shall be properly cleaned and disinfected to prevent cross-infection and the build-up of disease carrying organisms. Faeces, urine and uneaten or split feed shall be removed as often as necessary to minimize smell and to avoid attracting insects or rodents.*

The list of approved substances for cleaning and disinfection of buildings and installations for animal production includes "cleaning and disinfection products for teats and milking facilities." However, the rule does not explicitly describe the restrictions of use for available teat dip substances (EC, 2008). It is therefore uncertain whether European regulations allow the use iodine as an external antimicrobial substance (e.g., teat dip) in organic livestock production.

Japanese Ministry of Agriculture, Forestry, and Fisheries

According to Article 4 of the Japanese Agricultural Standard for Organic Livestock Products, "milking equipment and utensils are properly cleaned and disinfected, without using agents other than those for cleaning or disinfecting teats and those indicated in Attached Table 4." Iodine agents are included as allowed substances in "Attached Table 4" of the Japanese organic livestock standards – Agents for cleaning or disinfecting housing for livestock (JMAFF, 2005).

International Federation of Organic Agriculture Movements

Iodine is included in Appendix 5 of the IFOAM Norms as a substance allowed for pest and disease control and disinfection in livestock housing and equipment (IFOAM, 2014).

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

Evaluation Question #1: Indicate which category in OFPA that the substance falls under: (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) Iodine disinfecting agents are employed in livestock production to kill and prevent the spread of bacterial organisms associated with bovine mastitis, thus may be considered a livestock medicine. Iodine is also a required micronutrient for livestock, and animal feeds are typically fortified vitamin and mineral supplements containing various forms of iodine.

(B) The iodophor ethoxylated nonylphenol complex with iodine (CAS# 11096-42-7) was included on EPA List 3 – Inerts of unknown toxicity (US EPA, 2004b). Related iodine detergent complexes are exempt from the requirement of a tolerance for residues in egg and poultry products when used as sanitizers in poultry drinking water (40 CFR 180.1022). In addition, residues of iodine from the use of iodine and iodophor disinfectants are exempt from the requirement of a tolerance under 40 CFR 180.940. See "Legal Uses of the Substance" for details regarding the tolerance exemptions for iodine.

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)).

The production of iodine used in teat disinfection products entails two separate processes: iodine production and product formulation, often using a nonionic surfactant. Summarized below are the various methods used to generate iodine from natural sources and the transformation of insoluble molecular iodine to soluble antimicrobial mixtures.

Iodine Production

Molecular iodine (I_2) production processes generally utilize raw materials containing iodine, including seaweeds, mineral deposits, and oil well or natural gas brines. Oxidation of iodides extracted from dried and burned seaweed to produce iodine began in 1817 and continued until 1959. Initially developed on an industrial scale in the 1850s, modern commercial production methods involve the formation of iodine as a byproduct of sodium nitrate and brine processing.

Sodium Nitrate Process: Iodine can be obtained on an industrial scale as a byproduct of sodium nitrate production. Specifically, crushed nitrate ores and deposits known as "Caliche" are leached to give a solution containing sodium nitrate ($NaNO_3$) and calcium iodate [$Ca(IO_3)_2$]. After removal of sodium nitrate by precipitation, the iodate rich mother liquor is split and the larger fraction treated with a reducing agent, such as sulfur dioxide (SO_2) or sodium bisulfite ($NaHSO_3$), to reduce the iodate (IO_3^-) to iodide (I^-) (equations 1 and 2). Following the reduction reaction, the larger fraction containing iodide is combined with the remaining mother liquor containing iodate (i.e., smaller fraction), which generates free iodine (equation 3). The precipitated iodine is removed by filtration, water-washed, melted under pressure at 120 ^oC, and subjected to sulfuric acid drying. Once purified, the iodine is solidified and scraped into flakes for commercial use. Variations of this method using less concentrated iodide fractions are employed in the industrial production of iodine (Lauterbach & Uber, 2011; Lyday, 2000).

$$IO_3^- + 3\ SO_2 + 3\ H_2O \rightarrow I^- + 3\ H_2SO_4^{2-} \quad \text{(equation 1)}$$

$$2\ IO_3^- + HSO_3^- \rightarrow 2\ I^- + 3\ SO_4^{2-} + 3\ H_2SO_4 \quad \text{(equation 2)}$$

$$5\ I^-\ (\text{large}) + IO_3^-\ (\text{small}) + 3\ H_2SO_4 \rightarrow 3\ I_2 + 3\ H_2O + 3\ SO_4^{2-} \quad \text{(equation 3)}$$

Brine Process: Iodine is present in subsurface brines as sodium and/or potassium iodide, with natural concentrations ranging from about ten to 300 parts per million (ppm). Numerous industrial processes have been developed for both the oxidation of iodides in brines and recovery of the formed iodine from the reaction mixtures.

First used in Japan, the blowing-out process is the most widely used method for producing iodine from brines containing dissolved iodide. In general, the blowout process is divided into brine cleanup, oxidation of iodide (I^-) to iodine (I_2) followed by air blowing and recovery, and iodine finishing for commercial applications. Brine cleanup consists of skimming and settling steps to free the solution from oils, clays and other impurities. Sulfuric acid (H_2SO_4) or hydrochloric acid (HCl) is then added to the purified brine to achieve a pH of less than 2.5 since iodine (I_2) is more soluble and therefore more likely to be liberated under acidic conditions during the oxidation reaction. Once clarified and acidified, the brine is subjected to an excess of gaseous chlorine (Cl_2) resulting in oxidation of the dissolved iodide (I^-) to iodine (I_2) (equation 4). The I_2 formed in the oxidation reaction remains soluble, but is extracted from the brine using a countercurrent air blowout process. At this point, the iodine (I_2) is reduced to iodide (I^-) using sulfur dioxide (SO_2) and absorbed into solution (equation 5). This iodide is then treated with another round of Cl_2, which precipitates crystals of I_2. Sulfuric acid purification and processing methods similar to those described in "sodium nitrate processing" are then applied to the iodine obtained from the blowout process (Lauterbach & Uber, 2011; Lyday, 2000).

$$2\ I^- + Cl_2 \rightarrow I_2 + 2\ Cl^- \quad \text{(equation 4)}$$

$$I_2 + SO_2 + H_2O \rightarrow 2\ H\text{-}I + H_2SO_4 \quad \text{(equation 5)}$$

In the case of brines with lower iodide concentrations, the activated carbon recovery method can lead to greater recovery of the desired iodine. This method begins with treatment of acidified brine (see above) containing iodide (I^-) with sodium nitrite to generate iodine (I_2). The free iodine in solution is recovered by adsorption on activated carbon. Once adsorbed, the iodine is extracted from activated carbon using a hot solution of sodium hydroxide (NaOH) to obtain a solution of iodine in the form of iodate (IO_3^-) and iodide (I^-). Treatment of the iodate-iodide mixture with sulfuric acid (H_2SO_4) and potassium dichromate ($K_2Cr_2O_7$) leads to precipitation of iodine (I_2) crystals, which are removed by filtration. Iodine purification and processing for this recovery method requires pressing the iodine crystals into a cake and subliming or melting, treating with H_2SO_4 and flaking, as described in the previous section (Lauterbach & Uber, 2011).

Newer processes utilize ion-exchange resins to adsorb iodine from brines that have already undergone the oxidation reaction. In this method, the free iodine in solution is adsorbed on an anion-exchange resin packed into an adsorption column. Once saturated with iodine, the resin within the column is eluted using a caustic solution of sodium hydroxide (NaOH) in water followed by aqueous sodium chloride (table salt). The regenerated resin may be reused in adsorption columns for subsequent iodine recovery operations. The filtrate, which is rich in iodide (I^-) and iodate (IO_3^-) ions, is acidified with sulfuric acid or hydrochloric

acid and oxidized with chlorine gas to precipitate iodine. Purification and processing of the collected iodine follows a similar procedure to that described in previous sections (Lauterbach & Uber, 2011).

Iodine Mixtures and Complexes

Due to the limited water solubility of elemental iodine alone, numerous formulations of iodine with carriers and solubilizing agents have been developed to increase the solubility and therefore germicidal activity of aqueous iodine solutions. The mixture of one part elemental iodine (I_2) and two parts potassium iodide (KI) in water known as Lugol's iodine produces the soluble triiodide anion (I_3^-), which allows for a stable, low-level concentration of I_2 in solution (FDA, 2013a). Likewise, tincture of iodine solutions are produced as one-to-one mixtures of I_2 and KI in ethanol and water. The moderate solubility of I_2 in ethanol reduces the amount of KI required to solubilize I_2 in the aqueous mixture (Block, 2001).

The most commonly used teat disinfectants consisting of germicidal iodine are the iodophor products. According to the Merck index, the term "iodophor" may be applied to any product in which surface-active agents (surfactants) act as carriers and solubilizing agents for elemental iodine (I_2). Commonly used surfactants in iodophor products include polyvinylpyrrolidone (PVP) (Shetty, 1978) and alkyl phenyl ethoxylates, such as nonylphenol ethoxylates (NPEs) (Corby, 2001).

The basic method for preparing an iodophor is to bring elemental iodine into contact with the polymeric surfactant, such as those described previously, either in dry form or in the presence of a suitable solvent (Shetty, 1978). Iodophor complexes have also been prepared through the addition of iodine from Lugol's solution or tincture of iodine (described above) to an aqueous solution of the polymeric surfactant carrier (Austin & Hans, 1955). The resulting iodophor contains iodine in three forms: free iodine (I_2), iodide ion (I^-) and iodine loosely bound to the surfactant. Whether initially prepared in solution or dissolved in water following a dry mixing process, an equilibrium is established between the bound and free forms of iodine such that additional molecules of iodine are released into solution from the complex as available free iodine is consumed through germicidal activity (equation 6) (Corby, 2001). In addition to the solubilizing surfactant, iodide (I^-) generated *in situ* during the complexation reaction likely enhances the solubility of iodine (I_2) in aqueous solution, potentially in the form of triiodide ion (I_3^-) for some surfactant-iodine complexes. Newer production methods involve the incorporation of iodide (e.g., KI) and potentially other halide salts (bromides and chlorides) into the iodophor reaction mixture in order to avoid the reduction of expensive I_2 to I^- and help solubilize the available I_2 (Foret & Helming, 2009).

$$I_2 + \text{Carrier/Surfactant} \rightleftharpoons \text{Iodophor Complex} \qquad \text{(equation 6)}$$

Aqueous solutions of iodophors are generally acidic (pH between 2 and 4). Sodium bicarbonate ($NaHCO_3$) has been used to raise the pH of iodophor solutions; however, the available I_2 content becomes depleted with concomitant increase in the concentration of iodide ion (I^-) within a few weeks at neutral pH (i.e., pH of 7) (Hosmer, 1958). It is therefore unlikely that such additives are used in commercially available iodophor formulations. The adjustment of pH has also been used as an effective strategy for iodophor complex formation. For example, iodophors have been prepared through the dissolution of molecular iodine (I_2) in an alkaline solution of sodium hydroxide (NaOH) to generate iodide (I^-) and iodate (IO_3^-) ions, followed by acidification of the solution using hydrochloric acid (HCl) or sulfuric acid (H_2SO_4) in the presence of an appropriate surfactant carrier (Corby, 2001). Acidification of the solution containing I^- and IO_3^- regenerates I_2, which is intercepted and stabilized in the presence of the surfactant. Phosphate (PO_4^{3-}) or citrate ($C_6H_5O_7^{3-}$) buffers may be incorporated in some commercial iodophor formulations to maintain a pH between five and seven in the aqueous teat dip solutions (Rivera, 1988).

<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)).

According to USDA organic regulations, the NOP defines synthetic 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). Iodine in the form of iodide (I^-) and iodate (IO_3^-) salts is commonly extracted from subsurface brines and nitrate ores, respectively. However, molecular iodine (I_2) used in disinfectants, and bovine teat dips in particular, is recovered from these natural sources through various chemical processing using synthetic reagents, including mixing reactions

and oxidation-reduction reactions. Likewise, molecular iodine produced synthetically from naturally occurring forms of iodine is typically mixed with polymeric surfactant carriers and potentially other synthetic chemicals in the production of commercial iodophor complexes. While it is unlikely that chemical oxidants/reductants and other reagents used in the extraction of iodine from natural sources will persist, the surfactant carrier and any buffering agents (acids and salts) used in in the formulation process will necessarily remain in the iodophor product. Based on NOP definitions, it can therefore be concluded that iodine used in mastitis control products is synthetic.

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

The volatility of molecular iodine (I_2) and some organic forms of iodine (e.g., methyl iodide) is responsible for the facile transfer of iodine between the atmosphere, ocean and soil surfaces. When released to the atmosphere, I_2 can undergo photochemical conversions to reactive iodine radicals and ultimately other gaseous and particulate forms of iodine. Inorganic particulates containing iodine make of approximately 25% of iodine in the atmosphere, while 40–80% of atmospheric iodine consists of organic forms of iodine. The residence times for iodine in the atmosphere are 14 days for particulates, 10 days for inorganic gases (i.e., I_2) and 18 days for organic gases such as methyl iodide (ATSDR, 2004). Gaseous I_2 and particulate forms of atmospheric iodine are deposited onto oceans and land surfaces through wet and dry deposition. Evaporation of iodine from the land surface to the atmosphere is only about one percent of the amount transferred from the atmosphere to the land surface at any given time.

Various fate processes also dictate the distribution and speciation of iodine in water and soil. Iodine is cycled to the ocean through groundwater and river effluent. Microbial action converts iodide ions (I^-) to organic forms of iodine (i.e., methyl iodide), which volatilizes from surface water due to the limited solubility and favorable vapor pressure (ATSDR, 2004). In addition, iodide ions (I^-) are readily taken up into plant roots and gaseous molecular iodine (I_2) is absorbed through the leaves of plants. It therefore follows that both the deposition of particulate iodine onto plant surfaces and the direct update of iodine into plants factors into the transfer of iodine through the "soil-plant-cow-milk pathway." However, iodine levels in animal feeds resulting from vitamin and mineral supplementation will likely exceed the amounts absorbed by plants used to produce commercial animal feeds. Iodine accumulates to varying degrees in aquatic organisms, with bioaccumulation factors (BCFs) in algae ranging from 40 in fresh water to 4,000–10,000 in salt water (ATSDR, 2004). Certain seaweeds and algae are capable of concentrating iodine to levels as high as 0.8–4.5 g/kg of dry material, depending on the iodine concentration in surrounding seawater. In accordance with the K_{ow} of 309, iodine is less likely to bioaccumulate in aquatic organisms, such as fish (Bioconcentration Factor = 10–20) (ATSDR, 2004). Naturally occurring iodide (I^-) in water is largely oxidized to molecular iodine (I_2) during water treatment (WHO, 2003).

In contrast to molecular iodine described above, iodine in iodophor complexes is not likely to volatilize due to its association with the surfactant carrier and therefore a lowering of the vapor pressure. Specifically, when iodine (I_2)/iodide (I^-) are used with surfactant carrier molecules to form iodophors, the vapor pressure of pure iodine (0.3 mm Hg) decreases to 6.6×10^{-6} mm Hg (US EPA, 2005). The volatilization of iodophor iodine from water and soil is therefore dramatically reduced relative to free iodine. Iodine and iodophors are generally immobile to moderately mobile in soils. The anionic iodide (I^-) and iodate (IO_3^-) forms of iodine exist in water, and iodophor mixtures are not likely to contaminate ground or surface water for the allowable use patterns as disinfectants in medical and livestock production settings (US EPA, 2005).

The available literature suggests that some pharmaceutically active compounds originating from human and veterinary therapy are not eliminated completely in municipal water treatment plants and are therefore discharged into receiving waters. In general, conventional wastewater treatment methods were not designed to remove many of these iodine-containing drugs from the effluent. There is also concern that certain organic waste compounds containing iodine may be degrading to new and more persistent compounds that may be released instead of or in addition to the parent compound. According to peer-reviewed studies, several polar pharmaceutical compounds containing iodine can leach through subsoils into aquifers (HSDB, 2006).

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)).

Iodine is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3) that regulate important biochemical reactions, including protein synthesis and enzymatic activity, and help regulate metabolism, immune function, and fetal and child development (NIH, 2011). Because of these vital functions, a variety of processed foods are fortified with iodine to facilitate intake of the recommended daily allowance of the essential mineral in the general population. However, high intakes of iodine can cause many of the same symptoms associated with iodine deficiency, including goiter, elevated thyroid stimulating hormone levels, and hypothyroidism. The National Academy of Sciences established iodine Upper Intake Levels (ULs) representing the maximum amount of iodine that individuals from different age groups should consume per day to avoid adverse health effects from excess dietary iodine (NIH, 2011). For most people, iodine intakes from foods and supplements are unlikely to exceed the ULs.

Table 2. Tolerable Upper Intake Levels (ULs) for Iodine

Age	UL (µg/day)
1–3 years	200
4–8 years	300
9–13 years	600
14–18 years	900
19+ years	1,100

Data Source: NIH, 2011.
µg = microgram (one-millionth of a gram)

In general, iodine compounds range from low to moderate toxicity on an acute exposure basis and can be irritating to the skin. With an LD_{50} (dose at which 50% of test animals die) of 315 mg/kg in rats, iodine is considered moderately toxic (Toxicity Category II) to mammals through the acute oral route of exposure. Likewise, iodine is moderately toxic to mammals via inhalation based on the iodine concentration in air that leads to death of 50% of test rats (LC_{50} = 0.363 mg/L). While iodine is a primary dermal irritant (Toxicity Category I), the acute systemic toxicity of iodine via the dermal route of exposure is low (Toxicity Category III). Iodine is not considered a dermal sensitizer based on studies using guinea pigs (US EPA, 2006b).

The potential for neurotoxicity from exposure to elevated iodine levels has also been evaluated. Because thyroid hormones are essential to the development of the neuromuscular system and brain, iodine-induced hypothyroidism (underactive thyroid gland) can result in delayed or deficient brain and neuromuscular development in susceptible newborns. Older children and adults with iodine-induced hypothyroidism are unlikely to experience deleterious effects on the neuromuscular system. In sensitive individuals, oral exposure of excess stable iodine can also produce hyperthyroidism (overactive thyroid gland). Sensitive individuals include those who are initially iodine deficient, those who have thyroid disease (i.e., Graves disease associated with overproduction of thyroid hormones), those previously treated with antithyroid drugs, and those who have developed thyrotoxicosis (excess of thyroid hormones in the body) from drugs, such as amiodarone or interferon alpha treatments. Although thyrotoxicosis is associated with various neuromuscular disorders, these adverse effects are not likely to occur in iodine-induced hyperthyroidism, except in sensitive individuals already predisposed to neurological problems (US EPA, 2006b).

A limited number of open literature studies evaluating the potential developmental toxicity of iodine in mammals are available. Arrington et al. (1965) administered dietary iodine as sodium or potassium iodide to rats at doses of 0, 30, 60, or 120 mg/kg/day on gestation days 6–15. Decreased fetal body weight was the only effect observed in this study and only occurred at the highest dose tested. In another study, Lee and Satow (1989) administered potassium iodide by gavage (forced feeding) to Donryu rats at doses of approximately 75, 300, 900, 1500, or 1800 mg/kg/day. While an increased incidence of resorptions at 300 mg/kg and developmental anomalies were reported in treated rats, no data was available in this abstract to verify the reported effects and no discussion was provided on parental toxicity. In a more recent study, Balb/C mice were dosed with iodine at levels of 0, 1500, 6000, 12,000, and 24,000 micrograms per liter

(μg/L) in drinking water for four months prior to mating (Yang, 2006). Thyroid hormone levels in dams were altered relative to controls when iodine doses reached 3,000 μg/L, and an increased number of fetal resorptions and dead fetuses were observed in all treatment groups relative to controls. Because of the high concentrations of iodine utilized in this study, it can only be concluded that exposure to maternally toxic doses of iodine may lead to developmental effects (Yang, 2006). According to US EPA (2006b),

> *The Antimicrobials Division's Toxicity Endpoint Selection Committee (ADTC) concluded that there is no concern for increased susceptibility of infants and children to the exposures from antimicrobial uses of iodine and iodine complexes. Therefore, the [Food Quality Protection Act] Safety Factor has been removed (i.e., reduced to 1X) for iodine and iodophor complexes. This determination is based upon the following observations: (1) the available hazard data show no evidence of increased susceptibility to developing offspring, (2) the chronic Minimal Risk Level as determined by ATSDR (0.01 mg/kg/day) is based upon exposure of groups of children, the effects being subclinical hypothyroidism, a reversible condition, (3) the MRL value itself (0.01 mg/kg/day) is higher than the National Academy of Sciences recommended daily allowance of 0.0021 mg/kg/day for a 70 kg adult and 0.006 mg/kg/day for children ages 1–8 years. By definition, no adverse effects are expected below the MRL, and (4) the tolerable upper limit for children is estimated at 0.01–0.04 mg/kg/day for children ages 1–13 years. This value is in excess of the estimated dietary exposures occurring from the [antimicrobial] uses of iodine. It should also be noted that the lower end of the tolerable upper limit for children is equal to the MRL.*

In addition to iodine, the surfactants used to produce iodophor complexes have been specifically evaluated in mammals. The propoxyethoxy copolymers are poorly absorbed through intact skin and exhibit no toxic effects following single or repeated dermal applications even at the highest doses applied (2 g/kg to greater than 20 g/kg in acute studies and up to 10 g/kg/day in subchronic studies). Likewise, alkylphenol polyethoxylates (APEs), such as the widely used nonylphenol ethoxylate (NPE) carriers, are poorly absorbed through skin and show no toxicity via skin contact (US EPA, 2006b). NPEs with only one or two ethylene oxide units are generally more toxic than higher molecular weight NPEs, and readily break down to nonylphenol, a persistent organic compound and suspected endocrine disruptor (Soares, 2008). According to industry and peer-reviewed studies, NPEs are also highly toxic to aquatic organisms (US EPA, 2010). Lastly, animal studies of the polyvinylpyrrolidone (povidone) carrier indicate that the polymer is poorly absorbed from the gastrointestinal tract and is virtually non-toxic on an acute oral basis (LD_{50} = >40 g/kg). Exposure to povidone did not result in cancer in studies of up to two years in duration at intakes up to ten percent of the diet (US EPA, 2006b).

The ecological toxicities of iodine and, in some cases, iodophors have been investigated in birds, fish and aquatic invertebrates. With LD_{50} values ranging from >250 to >2,000 mg/kg for Northern bobwhite quail dosed with iodine, the available studies indicate that iodine is moderately toxic to practically non-toxic to avian species through the acute oral route of exposure (US EPA, 2006c). In addition, studies evaluating the subacute toxicity of iodine and iodophor complexes such as nonylphenoxypolyethody-ethanol-iodine in Bobwhite quail produced LC_{50} values in excess of 5,000 parts per million (ppm) and No Observed Effect Concentrations (NOECs) of 562 ppm or greater, indicating minimal potential for toxic effects in birds (US EPA, 2006c). Iodine is highly toxic to freshwater fish (Bluegill sunfish, LC_{50} = 0.61 mg/L) and aquatic invertebrates (Waterflea, NOEC = 0.09 mg/L). Chronic toxicity testing in aquatic organisms is not required for iodine and iodophors because all of the currently registered uses are indoor applications (US EPA, 2006c).

<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 the volatile nature of molecular iodine and its long history of production, transport and use as an antimicrobial agent, releases of iodine to the environment are inevitable. Atmospheric iodine can combine with water molecules and precipitate into water or soils (wet deposition). Based on the reported water solubility (approximately 0.3 mg/L at 20 ^{o}C), molecular iodine should preferentially adsorb to organic matter in soil with slow percolation into ground water and/or run off to surface waters (ATSDR, 2004). Plants that grow on these soils will absorb various forms of iodine through their roots and leaves, and animals will absorb iodine from these plant materials. Iodine readily vaporized from surface water to re-enter the atmosphere. The fact that various forms of iodine are ubiquitous in the environment suggests

that the small amounts of iodine released through use of iodine and iodophor disinfectants are unlikely to result in widespread environmental contamination.

In contrast to iodine itself, the chemical reagents used to process and manufacture iodine and iodine compounds could lead to environmental contamination if mishandled. For example, sulfur dioxide (SO_2) used as a reducing agent in iodine processing is a key atmospheric pollutant and contributor to the formation of acid rain (US EPA, 2012; Alberta, 2003). Likewise, the release of strong acids and bases used in the production of molecular iodine and, potentially, commercial iodophor complexes 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 iodine production facilities have been reported.

Evaluation Question #7: 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)).

Chemical interactions with iodine are possible during production formulation and use in dairy operations. Regarding iodophor production, molecular iodine (I_2) is intentionally reacted with polymeric nonionic surfactant carriers to stabilize the bulk of available iodine in the form of an iodine-surfactant complex leaving minor quantities of free iodine available in solution for antimicrobial action. Many of the iodophors commonly used for disinfection in the dairy industry consist of iodine mixed with polymeric nonionic surfactants, such as the nonylphenol ethoxylates, polyalkylene glycol and polyvinylpyrrolidone carriers..

While the chemical interaction/combination of iodine with surfactant carriers is not associated with toxicity, breakdown of certain NPEs may lead to toxic effects in treated livestock and applicators. Specifically, NPEs with only one or two ethylene oxide units more readily degrade to nonylphenol, an aquatic toxicant and suspected endocrine disruptor (US EPA, 2010; Soares, 2008). The nonionic carriers used to stabilize and solubilize iodine also act as detergents and remove the protective oils from contacted skin. Conditioners have been included in product formulations to mitigate the adverse effects associated with removal of these natural oils. Specifically, moisturizers such as glycerin and propylene are normally added at concentrations ranging from two to ten percent of the product formulation (Universal, 2011; Nickerson, 2001). Lanolin may also be added to iodophor teat dip products as an emollient to replace natural oils lost from the affected skin of dairy cows (Nickerson, 2011).

Evaluation Question #8: 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)).

Commercial iodophors are bactericidal, virucidal, fungicidal and tuberculocidal at their recommended dilution rates (CDC, 2008). Indeed, it is well documented in the literature that iodine and iodophor complexes are effective against pathogenic bacteria, including the major mastitis pathogens *Streptococcus agalactiae*, *Mycoplasma bovis*, and *Staphylococcus aureus*. The antimicrobial mode of action of iodophor complexes is related to the ability of molecular iodine (I_2) to penetrate the cell wall of microorganisms quickly and disrupt the structure and synthesis of proteins and nucleic acids (CDC, 2008). In light of this universal antimicrobial mode of action, iodine is potentially toxic to beneficial soil bacteria, fungi and other microorganisms. For example, polyvinylpyrrolidone iodine (1% available iodine) exhibited biocidal activity within five minutes of contact for *Aspergillus fumigatus*, a soil fungus involved in carbon and nitrogen cycling (Tortorano, 2005). The latter result was obtained in the absence of soil, which would partially or fully deactivate iodine depending on the conditions. Our literature searches did not identify information concerning the toxicity of iodine to other soil organisms (e.g., earthworms and nematodes).

Nonionic surfactant carriers used in commercial iodophors are toxic to microorganisms present in agricultural soil and irritating to the skin of treated livestock. These surfactants exert antimicrobial activity by binding to various proteins and phospholipid membranes, which increases the permeability of membranes and vesicles. The resulting leakage of low molecular mass compounds (i.e., ions and amino acids) leads to cell death or damage (Ivanković & Hrenović, 2010). While possible, exposure of beneficial soil microorganisms is unlikely due to the controlled use of iodophor products in indoor milking facilities.

Natural protective oils are removed from the teat skin of treated livestock, which may lead to irritation in the absence of conditioners and moisturizers in the formulated iodophor product (Nickerson, 2011).

Information was not identified on the potential or actual impacts of iodine and iodophor complexes upon endangered species, population, viability or reproduction of non-target organisms and the potential for measurable reductions in genetic, species or eco-system biodiversity.

Evaluation Question #9: 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)).

Iodine readily cycles among terrestrial, aquatic and atmospheric compartments in the environment. The persistence of iodine in the atmosphere depends on the chemical form, with residence times of 10, 14 and 18 days for gaseous molecular iodine, iodine particles and organic iodine (e.g., methyl iodide), respectively. Microbial action converts iodide ions (I^-) to methyl iodide (CH_3I) for release to the atmosphere. Plants absorb various forms of iodine from the atmosphere and soil, while animals concentrate iodine from edible plant materials in their tissues and fluids (e.g., milk). Humans therefore obtain nutritional iodine from plant and animal products. Seaweeds and algae are capable of concentrating iodine to levels as high as 0.8–4.5 g/kg of dry material, depending on the iodine concentration in surrounding seawater. Bioaccumulation of iodine in aquatic animals is not likely based on the reported K_{ow} of 309 (ATSDR, 2004).

Ecological impairment resulting from the allowed use of iodine is possible but unlikely. Despite the inherent toxicity of iodine to fish and aquatic invertebrates (US EPA, 2006c), the likelihood of adverse impacts is low due to the controlled, small volume use of these substances as teat antiseptics in indoor dairy operations. Iodine, iodophors and nonionic surfactants used in iodophors are potent microbiocides; large volume spills of these substances could therefore damage or kill beneficial soil microorganisms (bacteria, fungi and nematodes) (Tortorano, 2005; Ivanković & Hrenović, 2010). This type of accidental spill is unlikely considering controlled, low volume use of iodophor teat dips in dairies. If mishandled, the chemical reagents used in the processing of iodine could lead to environmental contamination in the form of acid rain from sulfur dioxide (SO_2) releases and dramatic alterations of soil and water pH from the release of strong acids and bases. Our literature search did not identify reports of environmental contamination related to the industrial production of iodine or iodophors.

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)).

Dermal contact is the most relevant route of exposure for iodine and iodophor disinfectants, especially those used for teat antisepsis in dairy operations. While concentrated iodine can be highly irritating to the skin, the acute systemic toxicity of iodine through dermal absorption is low (Toxicity Category III). Iodine is considered moderately toxic (Toxicity Category II) based on an LD_{50} of 315 mg/kg in rats. Symptoms of developmental toxicity have been observed in rodents at high doses of iodine over an extended period of exposure (up to four months); however, it is unclear how these effects translate to subchronic exposure to iodine through skin contact. US EPA determined that "there is no concern for increased susceptibility of infants and children to the exposures from antimicrobial uses of iodine and iodine complexes" (US EPA, 2006b). Although nonylphenol ethoxylates (NPEs) and their breakdown products can be toxic via the oral route of exposure, these surfactant carriers are poorly absorbed through skin and have not exhibited toxicity via dermal contact (US EPA, 2006b).

Since approximately 90% of iodine in the body residues in the thyroid, human health studies have mainly focused on adverse thyroid effects (US EPA, 2006b). Thyroid function is primarily regulated by thyroid-stimulating hormone (TSH), which is secreted by the pituitary gland for control of thyroid function and secretion of thyroid hormones thyroxine (T4) and triiodothyronine (T3). In this way, TSH helps protect the body from hypothyroidism (reduced thyroid activity, low T4 and T3 levels) and hyperthyroidism (increased thyroid activity, high T4 and T3 levels) (NIH, 2011). TSH levels may become elevated in the absence of sufficient iodine, thus leading to goiter, an enlargement of the thyroid gland that reflects the body's attempt to intercept more iodine from circulation to produce thyroid hormones. Reversible hypothyroidism, elevated TSH, and enlarged thyroid gland (goiter) can also occur in healthy individuals as

a protective response to excess iodine intake over an extended period of time (NIH, 2011). Iodine-induced hyperthyroidism has occurred in some individuals, particularly when iodine is administered to treat iodine deficiency (NIH, 2011).

Human studies have confirmed that excessive dietary iodine intake can decrease the serum concentrations of one or both thyroid hormones (T3 and T4) and increase TSH serum levels in healthy individuals. A fourteen-day oral toxicity study in euthyroid (healthy thyroid) human males showed that a moderate daily dose of 500 µg iodine/day did not alter hormone levels in serum, while higher iodine doses (1,500 and 4,500 µg iodine/day) led to depression in serum T4 with concomitant increase in serum TSH. US EPA established a No Observed Adverse Effect Level (NOAEL = 500 µg iodine/day) and a Lowest Observed Adverse Effect Level (LOAEL = 1,500 mg iodine/day) based on reversible subclinical hypothyroidism observed in several human studies (US EPA, 2006b). Based on the experimental NOAEL (500 mg/day) and the estimated dietary background iodine intake (200 µg/day), the Agency for Toxic Substances and Disease Registry (ATSDR) determined an acute (1–14 days) Minimum Risk Level (MRL) for iodine of 700 µg/day or approximately 10 µg/kg/day for a 70 kg (155 pound) person (ATSDR, 2004; US EPA, 2006b). It should be noted that this daily dose (700 µg/day) is within range of the Upper Intake Levels (ULs) established by the National Academy of Sciences for humans at various life stages (see Evaluation Question #5). Studies suggest that the elderly may be less tolerant of excess iodine than younger adults (ATSDR, 2004).

Chronic dietary exposure to excess iodine does not necessarily amplify the health impacts relative to acute and subchronic exposures. An eleven-year study evaluated the thyroid status of children ages 7–15 exposed to iodine in drinking water at concentrations of either 462 or 1,236 µg/L. All subjects were euthyroid with values for serum thyroid hormones and TSH concentrations within the normal range; however, TSH concentrations were significantly higher (33%) in the high iodine group. In addition, the high iodine group exhibited a 65% prevalence of goiter and 15% prevalence of Grade 2 (more severe) goiter compared to 15% for goiter and 0% for Grade 2 goiter in the low iodine group. Urinary iodine was 1,235 mg I/g creatinine in the high iodine group and 428 mg I/g creatinine in the low iodine group. The ATSDR (2004) human health chapter states the following:

> *Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the above urinary iodine/creatinine ratios are approximately equivalent to iodine excretion rates or steady state ingestion rates of 1,150 µg/day (29 µg/kg/day) and 400 µg/day (10 µg/kg/day) in the high and low iodine groups, respectively.*

Based on this chronic toxicity information, ATSDR established a chronic MRL for iodine of 10 µg/kg/day, which is equivalent to the acute MRL discussed earlier in this response (US EPA, 2006b; ATSDR, 2004). Chronic exposure studies have also been conducted to determine the relationship between stable (non-radioactive) iodine intake and thyroid cancer (ATSDR, 2004). Specifically, the results of retrospective studies using medical record data suggest that the incidence of thyroid cancer may increase in endemic goiter regions (i.e., regions with historically iodine-deficient populations) after dietary iodine supplementation. It is noted, however, that improved diagnosis in the more recent time periods is a confounding factor that may have contributed to the increased incidence of thyroid cancer (ATSDR, 2004). Overall, the risk of sustained chronic toxicity—including thyroid cancer—from excess iodine intake is low for healthy, iodine-sufficient individuals, but may be higher for sensitive and iodine-deficient populations.

One area of human health concern involves the chronic exposure to excess dietary iodine through milk consumption. Historically, possible sources of iodine in milk have included iodine supplements in dairy feeds, iodophor sanitizers used in dairy processing plants, iodophor teat dips used to control the spread of mastitis pathogens among dairy cows, and iodine-containing medications used by veterinarians (Bruhn, 1983). Feed supplementation appears to be the major contributor to high milk iodine levels for modern dairy operations following prudent teat dipping protocols.

Studies have shown that iodine concentrations in milk range from an average of 147.8 µg/kg for dairies that do not use iodine teat dips or backflushes to 166.7 µg/kg for dairies only using iodine teat dips, while the combination of iodine teat dips and backflushes significantly increases milk iodine concentrations to an average of 251.3 µg/kg (Bruhn, 1987). A more recent study reported similar milk iodine concentrations of 164 to 252 µg/kg, with the highest concentrations observed when pre-milking teat dips were applied and

incompletely wiped off before milking (Borucki Castro, 2012). Using lower concentration pre-dip solutions (0.1–0.5%), completely wiping teats before milking and avoiding the application of iodophor sprays can greatly reduce milk iodine concentrations (Borucki Castro, 2012; Galton, 1986). Even at the highest milk iodine concentration of 655 µg/kg reported by Borucki Castro (2012), average milk consumption of 1.5 cups/day for children ages 2-11 (USDA, 2010) provides a daily intake of iodine (230 µg/day) in the range of the ULs of 200–600 µg/day (NIH, 2011) and well below the chronic MRL of 700 µg/day (ATSDR, 2004).

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)).

Information regarding the availability of natural, non-synthetic agricultural commodities or products that could substitute for iodine and iodophor disinfectants is limited. Nisin, a naturally occurring antimicrobial protein known as a bacteriocin, has been incorporated into pre- and post-milking teat dips and is highly effective against Gram-positive as well as Gram-negative bacteria (Nickerson, 2001). Formulated products containing nisin, such as Wipe Out® Dairy Wipes, are currently available for mastitis prevention (Jeffers, 2014). Nisin naturally present in milk is also instrumental in preventing milk spoilage due to bacterial contamination (Ahlberg, 2012). The antimicrobial mode of action for nisin involves lysis of the cytoplasmic membrane phospholipid components (Nickerson, 2001).

Nisin, generally considered a natural product, is not listed as a prohibited non-synthetic substance in organic livestock production (7 CFR 205.604). However, the NOSB classified nisin as synthetic during their 1995 review of the substance for organic processing (USDA, 1995a). Nisin was not recommended for inclusion on the National List for use in the processing of food labeled as "organic" and "made with organic ingredients" (USDA, 1995b; OMRI, 2014).

Small-scale milk producers use homemade udder washes containing lavender essential oil, water, and apple cider vinegar (i.e., acetic acid) as the active antimicrobial agent (Weaver, 2012). Other procedures for pre- and post-milking treatments include an udder wash (warm water or warm water with a splash of vinegar) in combination with a teat dip (1 part vinegar, 1 part water, plus 3–4 drops Tea Tree oil per ounce). Naturally-derived acids (e.g., lactic acid) may be used as standalone germicides or further activated through the synergistic interaction with hydrogen peroxide to provide a bactericidal teat cleansing treatment (Belsito, 2012). In addition to the natural substances mentioned above, a small number of synthetic substances are currently allowed as disinfectants, topical treatments, and external parasiticides in organic livestock production (7 CFR 205.603 (a) and (b)):

- **Iodine**: Disinfectant, topical treatment, and/or parasiticide. A broad spectrum germicide, which is fast-acting and effective against all mastitis-causing bacteria as well as fungi, viruses, and some bacterial spores. It is microbicidal due to the oxidizing reaction between iodine and organic matter. Iodophors are produced when iodine is dissolved in aqueous solutions containing water-soluble detergents or surfactants (Nickerson, 2001).
- **Ethanol**: Disinfectant and sanitizer only, prohibited as a feed additive.
- **Isopropanol**: Disinfectant only.
- **Sodium hypochlorite**: Commonly referred to as commercial bleach. On the National List as a disinfectant, not a topical treatment option. It has been noted that such solutions are not marketed as teat dips and their use violates federal regulations; however, its use has continued for both pre- and post-milking teat dips at a 4.0% hypochlorite concentration (Nickerson, 2001).
- **Hydrogen peroxide**: On the National List as a disinfectant, not a topic treatment option. Provides a wide spectrum of control against most mastitis-causing bacteria through its oxidizing action.
- **Chlorhexidine:** Allowed synthetic on the National List 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.

Suppliers of livestock and dairy products have indicated that iodine is traditionally the preferred germicide used as a teat dip for mastitis prevention. Recent natural disasters in Japan and water shortages in Chile led to increasing prices for iodophor products and resultant interest in alternative teat dips (Animart, 2012). Goodwin *et al.* (1996) demonstrated that post-milking teat dips using chlorhexidine reduced the total

bacteria load in milk to a greater extent than similar treatments with a commercial iodophor. However, the small sample size (nine cows) is a limiting factor for this study. Animal health researchers recently found that acidified sodium chlorite (ASC)-chlorine dioxide solutions are equally effective in preventing new intramammary infections (IMI) in lactating dairy cows naturally exposed to mastitis pathogens when compared to an established iodophor teat dip product (Hillerton, 2007). Alternatively, the results of experimental challenge studies (cows intentionally exposed to mastitis pathogens) suggest that ASC may actually provide enhanced antimicrobial activity against the mastitis bacteria *Staphylococcus aureus* and *Streptococcus agalactiae* relative to a commercial iodophor (Boddie, 2000; Drechsler, 1990). These studies also indicate that the tested ASC products had no deleterious effects on teat condition. Further, ASC components exhibit minimal persistence in the environment and are highly unlikely to contaminate the milk from treated animals (USDA, 2013). Commercial ASC teat dips are being increasingly used in conventional dairies, and the NOSB is considering a petition to add this substance to the National List. (Ecolab Inc, 2012).

The available information suggests that commercial antimicrobial products containing oxidizing chemicals (e.g., sodium chlorite, hypochlorite, iodophor), natural products composed of organic acids (e.g., lactic acid), and homemade products using vinegar (i.e., acetic acid) as the active ingredient may all be equally effective teat dip treatments. For example, commercially available post-milking teat germicides containing Lauricidin® (glyceryl monolaurate), saturated fatty acids (caprylic and capric acids), lactic acid and lauric acid reduced new intramammary infections (IMI) in cows inoculated with *Staphylococcus aureus* and *Streptococcus agalactiae* at levels approaching those achieved using iodophor products (Boddie & Nickerson, 1992). Aging for five months at elevated temperature (40 ^{o}C) diminished the level of protection of the Lauricidin® formulation against new IMI. Although numerous active ingredients are formulated in pre- and post-dip products, iodine and iodophor products have a long history of supporting the health and productivity of milk-producing animals through effective mastitis control.

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

A number of control measures for contagious mastitis pathogens have been developed and successfully implemented in the dairy industry. Mastitis, an inflammation of the breast tissue, is typically caused by environmental pathogens, such as Gram-negative bacteria *Serratia spp.* (Petersson-Wolfe & Currin, 2011). Since these pathogens are commonly found in soil and plant matter, cows on pasture or housed on organic bedding experience heighted exposure to mastitis-causing pathogens. Damage of the teat ends and poor udder cleanliness may also increase the risk of spreading the pathogens throughout the herd. The risk of mastitis incidents is significantly reduced when producers maintain a clean and dry environment for the animals. Frequently changing the animal's bedding material and/or using inorganic bedding (i.e., sand) may also reduce environmental contamination with these bacteria (Petersson-Wolfe & Currin, 2011). In addition, providing a healthy, balanced diet to the animal and ensuring the cleanliness of milking implements are important steps for maintaining health udders.

Teat dips and udder washes are critical for preventing incidents of mastitis and virtually all milk producers apply some form of teat disinfectant post milking. Any mastitis control program will incorporate disinfecting teat dips at milking to prevent new infections and reduce the duration of existing infections. Cessation of hygienic milking practices, and particularly teat dipping, will allow bacterial populations on teat skin to propagate, thus increasing the risk of infection (Poock, 2011). While pre-dipping can be beneficial to animal health, post-dipping with an effective sanitizer is essential for both removing milk residue left on the teat and killing harmful microorganisms (Bray & Shearer, 2012). Overall, dairy professionals agree that teat dipping using a safe and effective disinfectant is vital to maintaining the health and productivity of milk-producing animals.

Alternative practices to teat dipping/spraying or udder washing are not advised, as the exclusion of a disinfecting step from a mastitis control program would significantly increase the likelihood of infection. Although alternative practices are not available, a number of alternative substances are presented in Evaluation Question #11.

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