United States Department of Agriculture
Agricultural Marketing Service | National Organic Program
Document Cover Sheet
https://www.ams.usda.gov/rules-regulations/organic/national-list/petitioned

Document Type:

☐ **National List Petition or Petition Update**

A petition is a request to amend the USDA National Organic Program's National List of Allowed and Prohibited Substances (National List).

Any person may submit a petition to have a substance evaluated by the National Organic Standards Board (7 CFR 205.607(a)).

Guidelines for submitting a petition are available in the NOP Handbook as NOP 3011, National List Petition Guidelines.

Petitions are posted for the public on the NOP website for Petitioned Substances.

☒ **Technical Report**

A technical report is developed in response to a petition to amend the National List. Reports are also developed to assist in the review of substances that are already on the National List.

Technical reports are completed by third-party contractors and are available to the public on the NOP website for Petitioned Substances.

Contractor names and dates completed are available in the report.

Silver Dihydrogen Citrate

Handling/Processing

Identification of Petitioned Substance

Chemical Names:
Silver Dihydrogen Citrate
Monosilver dihydrogen citrate
Monosilver citrate
Silver; 2-(carboxymethyl)-2, 4-dihydroxy-4-oxobutanoate

Other Name:
Citric acid and silver citrate
2-Hydroxy-1,2,3-propane tricarboxylic acid monohydrate and 2-hydroxy-1,2,3-propane tricarboxylic acid silver (1+) salt monohydrate

Trade Names:
SDC 2400
Silverion 2400
TINOSAN® SDC Active
TINOSAN® SDC lyophilisate
TINOSAN® SDC
FAT 81'034
FAT 81'033
Axenohl
C-1390

CAS Numbers:
No CAS Number available for SDC
77-92-9 (Citric Acid)
206986-90-5 (Silver Citrate hydrate)
14701-21-4 (Silver Ions; electrochemically generated)

Other Codes:
ELINCS number: 460-890-5

Summary of Petitioned Use

The petitioned substance, silver dihydrogen citrate, is intended to be used as an antimicrobial processing aid for the processing of poultry (carcasses, parts, and organs) and fruits and vegetables (except for citrus fruit and grapes intended for winemaking). Silver dihydrogen citrate is also intended to be used as a disinfectant and sanitizer for food processing equipment and food contact surfaces.

Characterization of Petitioned Substance

<u>Composition of the Substance:</u>
Silver dihydrogen citrate (SDC) is a stable mixture of citric acid monohydrate and silver dihydrogen citrate monohydrate. Silver dihydrogen citrate (citric acid and silver citrate) is a simple salt, wherein the silver ion is the positively charged ion and the dihydrogen citrate moiety is the negatively charged ion, possessing a negatively charged carboxylate group. This compound is present in a dissociated state in the solution, with the positively charged and negatively charged ions surrounded by water molecules. Typical solution composition of SDC is as follows in Table 1 (Pure Bioscience 2015).

Table 1: Silver Dihydrogen Citrate - Typical Solution Composition

Components	Wt %
Water (CAS No. 7732-18-5)	> 76
Citric Acid (CAS No. 77-92-9)	< 22
Silver Ions (CAS No. 14701-21-4; electrochemically generated)	0.24

Anhydrous silver dihydrogen citrate compositions are comprised of silver dihydrogen citrate and citric acid (Arata 2006). The anhydrous composition is prepared by freeze drying a frozen stock solution of silver dihydrogen citrate to yield a translucent, gray crystalline material that can be further ground into a fine powder.

Citric acid ($C_6H_8O_7$, CAS No. 77-92-9) is the compound 2-hydroxy-1,2,3-propanetricarboxylic acid. Citric acid is authorized by the Food and Drug Administration (FDA) for use as a direct food substance (21 CFR 184.1033). It is described as occurring as colorless, translucent crystals or as a white, granular to fine, crystalline powder. It is anhydrous or contains one molecule of water. The hydrous composition spontaneously loses water in dry air, resulting in their surface assuming a powdery appearance. It is odorless and has a strongly acidic taste. The Food Chemicals Codex (FCC) requires that the material assays at 99.5% to 100.5% (Pharmacopeia 2010). It is a naturally occurring constituent of plant and animal tissues (Pharmacopeia 2010).

Source or Origin of the Substance:

Silver dihydrogen citrate is a synthetic compound that can be produced by two general pathways: electrolytically or chemically. The production of silver dihydrogen citrate by electrolyzing silver metal results in the formation of silver dihydrogen citrate without any byproducts (Arata 2003, Arata 2006). Generally, silver dihydrogen citrate can be made by immersing silver electrodes in an aqueous electrolyte solution that contains citric acid. The aqueous electrolyte solution contains at least 5% citric acid, but usually approximately 10% citric acid (% wt./vol.). An electrolytic potential (12 V to 50 V) is then applied to the electrodes to provide a flow of silver ions. The silver ions then combine with citric acid to form silver dihydrogen citrate.

The chemical production methods use silver citrate (i.e., citric acid trisilver salt hydrate; $Ag_3C_6H_5O_7 \bullet X\ H_2O$; CAS No. 206986-90-5) as an intermediate substance. First, silver citrate can be produced in analytically pure form by three different processes outlined below (Djokić 2008).

(a) Sodium citrate ($Na_3C_6H_5O_7$; CAS No. 6132-04-3) in aqueous media:
$3\ AgNO_3 + Na_3C_6H_5O_7 \rightarrow Ag_3C_6H_5O_{7\,(s)} + 3\ NaNO_{3\,(aq)}$

(b) Sodium Hydroxide (NaOH; CAS No. 1310-73-2) in aqueous media:
$2\ AgNO_3 + 2\ NaOH \rightarrow Ag_2O_{(s)} + 2\ NaNO_{3\,(aq)} + H_2O_{(aq)}$
$3\ Ag_2O_{(s)} + 3\ H_3C_6H_5O_7 \rightarrow 2\ Ag_3C_6H_5O_{7\,(s)} + 3\ H_2O_{(aq)}$

(c) Ammonium Hydroxide (NH_4OH; CAS No. 1336-21-6) in aqueous media:
$AgNO_3 + 3\ NH_4OH \rightarrow [Ag(NH_3)_2]OH_{(aq)} + NH_4NO_{3\,(aq)} + 2\ H_2O_{(aq)}$
$3\ [Ag(NH_3)_2]OH_{(aq)} + 2\ H_3C_6H_5O_7 \rightarrow Ag_3C_6H_5O_{7\,(s)} + (NH_4)_3C_6H_5O_{7\,(aq)} + 3\ NH_4OH_{(aq)}$

Then, silver citrate is dissolved in concentrated aqueous solutions of citric acid forming silver dihydrogen citrate according to the following reaction (Djokić 2008):

(d) $Ag_3C_6H_5O_{7\,(s)} + n\ H_3C_6H_5O_{7\,(aq)} \rightarrow [Ag_3(C_6H_5O_7)_{n+1}]^{3n-}{}_{(aq)} + 3n\ H^+{}_{(aq)}$; where n = 2 or 1

The reaction is reversible, and the solution composition is dependent on the molar ratio of silver citrate and citric acid.

Properties of the Substance:

Physical and chemical properties of the substances are summarized in Table 2 and Table 3.

Table 2: Physical and Chemical Properties of Silver Dihydrogen Citrate (SCCP 2009).

Property	**Value**
CAS Reg. Number	N/A
ELINCS	460-890-5
Chemical formula	$AgH_2C_6H_5O_7 \cdot H_2O + H_3C_6H_5O_7 \cdot H_2O$
Molar mass	210 g/mol ($H_3C_6H_5O_7 \cdot H_2O$) and 317 g/mol ($AgH_2C_6H_5O_7 \cdot H_2O$)
Appearance	Translucent gray crystalline material (anhydrous)
Solubility, water	1 g in 1.1 mL (~ 88 g/100 mL)

Table 3: Physical and Chemical Properties of Citric Acid (Pharmacopeia 2010).

Property	**Value**
CAS Reg. Number	77-92-9
Chemical formula	$H_3C_6H_5O_7$
Molar mass	192.12 g/mol
Appearance	Colorless, translucent crystals/white crystalline powder
Solubility, water	1 g in 0.5 mL (~ 200 g/100 mL)
Solubility, alcohol	1 g in 2.0 mL (~ 50 g/100 mL)

Silver dihydrogen citrate is incompatible with aluminum sulfate, aluminum ammonium chloride, aluminum orthophosphate, chlorides, sequestering agents designed to remove transition metals from solution, ethylenediaminetetraacetic acid (EDTA, above 1.5%), and calcium hardness above 300 ppm. These substances are not on the National List for organic handling.

The petitioned substance is compatible with most metals including stainless steels. Ionic silver rapidly reacts with chlorides and other negatively charged ions that result in low solubility silver salts. This reaction would potentially affect stability of the product.

In addition to the petition substance, silver nanoparticles (Ag-NPs) are well-documented to possess high antimicrobial, antifungal, and antiviral properties and are frequently present in air/water filters, food containers, textiles, and other consumer products (Dubas et al. 2006, Tankhiwale and Bajpal 2009, Duncan 2011). Several explanations have been posited to explain the antimicrobial properties of Ag-NPs (Sondi and Salopek-Sondi 2004, Banerjee et al. 2010); however, the most likely explanation is the release of silver ions (Ag^+) which inhibit cell functions and can generate reactive oxygen species (Pal et al. 2007, Hsueh et al. 2015). The rate and extent of Ag^+ ion release from Ag-NPs is highly dependent on the physical properties of the colloidal nanoparticles, including size, shape, and capping agent (Dobias and Bernier-Latmani 2013). Thus, the addition of Ag-NPs to the petitioned substance could be added to augment the antimicrobial properties of SDC by increasing the concentration of Ag^+ ions. Studies would be required to determine the concentration and physical properties of Ag-NPs to be added to solutions of SDC for optimal antimicrobial efficiency. Conversely, the concentration of Ag^+ ions in solutions of the petitioned substance can be easily modulated in the synthesis and formulation steps of SDC.

Specific Uses of the Substance:

According to Food Contact Substance Notifications (FCN) 1569, 1600, and 1768, the primary uses of silver dihydrogen citrate in food processing are as a disinfectant and sanitizer for food processing equipment and food contact surfaces and as an antimicrobial agent in the processing of poultry (carcasses, parts, and organs) and fruits and vegetables. The petitioned substance is not permitted for the treatment of citrus fruit or grapes intended for winemaking.

Approved Legal Uses of the Substance:

The United States Department of Agriculture (USDA) Food Safety and Inspection Service (FSIS) has identified aqueous solutions of silver dihydrogen citrate as a food grade substance, approved in 21 Code of Federal Regulations (CFR) for use as an antimicrobial solution applied by spray or dip on poultry carcasses, parts, and organs [FSIS Directive 7120.1 Rev. 42; (USDA 2017)]. According to FCN 1768, aqueous solutions of silver dihydrogen citrate are permitted for use at levels up to 160 parts per million (ppm) silver dihydrogen citrate in the spray or dip applied to poultry carcasses, parts, and organs but are not permitted to be used in combination with any other silver containing antimicrobial or used in chiller baths (US FDA 2017). Aqueous solutions of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid (FCN 1569) are permitted for use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses, parts, and organs but are not permitted for use in combination with any other silver containing antimicrobial or used in chiller baths (US FDA 2015).

Aqueous solutions of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid (FCN 1600) are permitted for use as an antimicrobial solution applied by spray or dip on fruits and vegetables intended for processing. Aqueous solutions of silver dihydrogen citrate are permitted for use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to fruits and vegetables intended for processing (US FDA 2015). As a food contact surface sanitizer, aqueous solutions of SDC are not intended for use on any citrus fruit nor is it for use on grapes intended for winemaking nor for use in combination with any other silver containing antimicrobial.

The Environmental Protection Agency (EPA) has approved the petitioned substance for use as an antimicrobial, disinfectant, fungicide, and virucide, and food contact surface sanitizer (see EPA Registration Nos. 72977-1, 72977-3, 72977-4, 72977-5, and 72977-6). The substance is the subject of an exemption from tolerance for residues of silver in foods from food contact surface and processing equipment sanitizing applications (40 CFR 180.950).

Silver dihydrogen citrate has been reviewed and certified by NSF International for use as a food contact surface sanitizer and is listed on the Non-Food Compounds White Book, Category D2, "Sanitizers that do not always require a rinse."

<u>Action of the Substance:</u>
The silver ion is well known to be effective against a broad range of microorganisms. The antimicrobial action of silver ions is multifaceted due to strong interactions with the purine and pyrimidine DNA bases and thiol groups (i.e., -SH or sulfhydryl groups) present in enzymes and proteins within the microorganism (Izatt et al. 1971, Bragg and Rainnie 1974). These interactions markedly inhibit bacterial growth (Richards et al. 1984). Silver ions inhibit cell division, damage the cellular envelope, and create structural abnormalities that ultimately result in microbial death (Jung et al. 2008).

The citrate counter ion also significantly contributes to the efficacy of the silver ions antimicrobial properties. Citrate ions stabilize the ionic form and antimicrobial properties of silver(+1), as they do not show a tendency to be oxidized by silver ions (Ag^+) which results in Ag^o (Djokić 2008). Citric acid is a major constituent of the Kreb's cycle, providing many precursors required for energy metabolism. It is readily recognized by bacteria as either a sole source of carbon and energy or as a co-metabolite in the presence of a food source, such as glucose. Thus, bacteria have both passive diffusional and active transport mechanisms for incorporation of citrate, which increases the permeability of the antimicrobial silver ion when it serves as a citrate cofactor (MacDonald and Gerhardt 1958, Korithoski et al. 2005, Pudlik and Lolkema 2011, Mortera et al. 2013).

<u>Combinations of the Substance:</u>
Silver dihydrogen citrate is a formulation consisting of typically electrochemically generated silver ions, which form a complex with a citrate counterion and citric acid. Citric acid is used primarily as a stabilizer and pH control agent. Citric acid is also affirmed by the FDA (21 CFR 184.1033) as generally recognized as safe (GRAS) and may be used with no limitations other than good manufacturing practice. Sodium lauryl sulfate can be introduced intentionally during manufacturing to act as a solution stabilizer and is permitted for direct addition to food for human consumption by the FDA (21 CFR 172.822).

Status

<u>Historic Use:</u>
There are no historic uses of the petitioned substance in organic agricultural production or conventional agricultural production.

<u>Organic Foods Production Act, USDA Final Rule:</u>

Silver dihydrogen citrate is not listed in the Organic Foods Production Act of 1990 (OFPA) or the USDA organic regulations, 7 CFR Part 205.

International

Silver dihydrogen citrate has not been permitted or reviewed by international organizations with regards to organic standards for agricultural production.

Evaluation Questions for Substances to be used in Organic Handling

Evaluation Question #1: Describe the most prevalent processes used to manufacture or formulate the petitioned substance. Further, describe any chemical change that may occur during manufacture or formulation of the petitioned substance when this substance is extracted from naturally occurring plant, animal, or mineral sources (7 U.S.C. § 6502 (21)).

A process of making silver dihydrogen citrate is an electrolytic process (Arata 2003, Arata 2006). The process begins with preparation of an electrolyte solution, which is an aqueous solution comprised of citric acid. Water is purified by introducing it into a reverse osmosis unit and passing it through a semi-permeable membrane to remove impurities. Citric acid (anhydrous, 99% pure) is then mixed with the water. Citric acid solutions having citric acid concentrations in the range of about 1% (wt./vol.) to about the solubility limit of citric acid in water (about 60% wt./vol.) are suitable for preparing silver dihydrogen citrate solutions. A pair of silver electrodes (200 troy ounces of 999 fine silver) is immersed into the electrolyte solution at a suitable spacing to allow an ionic current to flow between them. An electrolytic potential is applied across the electrodes to create an ionic current flow between the electrodes. A suitable voltage is about 12 to about 50 volts. The resulting flow of ions through the electrolyte solution results in the production of an aqueous solution of silver dihydrogen citrate and citric acid. It is possible to recirculate the silver dihydrogen citrate solution through the electrolytic cell to increase the final concentration of silver dihydrogen citrate in the solution. The solution may then be used as prepared or stored (Arata 2003).

Citric acid may be produced by recovery from sources such as lemon or pineapple juice. Most prevalently, citric acid is produced by mycological fermentation using *Candida spp.* (21 CFR 173.160 and 21 CFR 173.165) and recovery from *Aspergillus niger* fermentation liquor by a solvent extraction process (21 CFR 173.280).

The aforementioned chemical routes using silver citrate (i.e., citric acid trisilver salt hydrate; $Ag_3C_6H_5O_7 \bullet X H_2O$; CAS No. 206986-90-5) as an intermediate can be used to produce aqueous solutions of the petitioned substance (Djokić 2008). However, this route is not used in commercial processes to manufacture or formulate silver dihydrogen citrate.

Evaluation Question #2: 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)). Discuss whether the petitioned substance is derived from an agricultural source.

Silver dihydrogen citrate is a synthetic material solely manufactured by a chemical process, not extracted from naturally occurring plant, animal, or mineral sources. Silver dihydrogen citrate is produced electrolytically, through the immersion of silver electrodes in an aqueous solution of citric acid. The ionic current flow between the electrodes reacts with the aqueous citric acid to produce an aqueous solution of silver dihydrogen citrate and citric acid. The petitioner does not describe how the citric acid used in manufacturing was made.

Evaluation Question #3: If the substance is a synthetic substance, provide a list of nonsynthetic or natural source(s) of the petitioned substance (7 CFR § 205.600 (b) (1)).

There are no known non-synthetic or natural sources of silver dihydrogen citrate (i.e., citric acid + silver citrate). The petitioned substance is created by a chemical process. Ionic current flow between silver electrodes in a solution of citric acid results in the formation of silver dihydrogen citrate.

<u>Evaluation Question #4:</u> **Specify whether the petitioned substance is categorized as generally recognized as safe (GRAS) when used according to FDA's good manufacturing practices (7 CFR § 205.600 (b)(5)). If not categorized as GRAS, describe the regulatory status.**

Silver dihydrogen citrate is not categorized as generally recognized as safe (GRAS). The USDA Food Safety Inspection Service has reviewed and approved silver dihydrogen citrate for use as a food contact substance in applications for treating poultry (FCN 1569 and FCN 1768) and fruits and vegetables (FCN 1600). The substance has been reviewed and approved by the EPA for use as an antimicrobial, disinfectant, fungicide, and virucide, and food contact surface sanitizer (EPA Registration Nos. 72977-1, 72977-3, 72977-4, 72977-5, and 72977-6). The substance is the subject of an exemption from tolerance for residues of silver in foods from food contact surface and processing equipment sanitizing applications (40 CFR 180.950).

Silver dihydrogen citrate has been certified by NSF International, an independent public health and safety organization, for use as a sanitizer on all surfaces and as not always requiring a rinse in and around food processing areas (NSF Registration No. 144518).

The petitioned substance has been added to the list of Safe and Suitable Ingredients Used in the Production of Meat, Poultry, and Egg Products by the USDA (FSIS Directive 7120.1 Rev. 42).

Citric acid is affirmed by the FDA (21 CFR 184.1033) as generally recognized as safe (GRAS) and may be used with no limitations other than good manufacturing practice. Sodium lauryl sulfate can be introduced intentionally during manufacturing to act as a solution stabilizer and is permitted for direct addition to food for human consumption by the FDA (21 CFR 172.822).

<u>Evaluation Question #5:</u> **Describe whether the primary technical function or purpose of the petitioned substance is a preservative. If so, provide a detailed description of its mechanism as a preservative (7 CFR § 205.600 (b)(4)).**

The primary technical function or purpose of silver dihydrogen citrate is for use as an antimicrobial for pathogen control in organic handling. Its intended uses are for (a) direct food contact (secondary direct food additive) in food production related to poultry carcass, organs and parts and fruits and vegetables (except for citrus fruit and grapes intended for winemaking); and for (b) indirect food contact surface sanitization. There is no published information to suggest that the petitioned substance is being used primarily as a preservative.

<u>Evaluation Question #6:</u> **Describe whether the petitioned substance will be used primarily to recreate or improve flavors, colors, textures, or nutritive values lost in processing (except when required by law) and how the substance recreates or improves any of these food/feed characteristics (7 CFR § 205.600 (b)(4)).**

There is no information to suggest that silver dihydrogen citrate is used to recreate or improve flavors, colors, textures, or nutritive values lost in the processing of agricultural products. The petition's request is to permit the use of SDC solutions as a processing aid in the wash and/or rinse water for direct and indirect food contact.

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

There is no evidence to suggest that aqueous solutions of silver dihydrogen citrate will affect the nutritional quality of the food or feed when it is used as intended. The major component, citric acid, is generally recognized as safe by the FDA (21 CFR 184.1033) and possesses no propensity for positive or adverse effects on the nutritional quality of food or feed when used as intended with the petitioned substance.

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

In the process for the manufacturing of the petitioned substance, no heavy metals or other contaminants in excess of FDA tolerances have been reported in the petitioned substance.

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

The environmental impacts of the product from its intended uses have been evaluated by both FDA and EPA. FDA reviewed the environmental impacts resulting from use in poultry and produce processing, while EPA reviewed the impacts as part of the pesticide registration process. During the treatment of the process water at on-site wastewater treatment facilities, the silver component is expected to partition to sludge (94 %) and waste water (6 %) with environmental introduction concentrations of 238 nanograms (ng)per liter (L) and 1.5 ng/L, respectively (US FDA 2015). The concentration of silver in the sludge is 20,000 times lower than the level requiring disposal as toxic waste (US FDA 2015). Furthermore, the concentration of silver in waste water is approximately 200 times less than naturally occurring levels of silver in the environment in surface waters (0.2-0.3 µg/L) and is not predicted to impact the natural variation of background silver (US FDA 2015). These environmental assessments, with the FDA's Findings of No Significant Impact (FONSI) concluded that silver dihydrogen citrate, when used as intended, does not present any significant environmental impacts.

Silver is classified by the EPA as a toxic hazardous waste if detected at 5 mg/L by Toxicity Characteristic Leaching Procedure-EPA method 1311 (EPA HW No. D011; 40 CFR 261.24). According to the 1992 Reregistration Eligibility Decision for silver (EPA-738-F-93-005), the EPA determined that the available acute toxicity data indicate that silver, which persists in the aquatic environment, is highly toxic to fish, aquatic invertebrates, and estuarine organisms. The active disinfectant ingredient, silver dihydrogen citrate (SDC), has an acute LC_{50} for freshwater fish that ranges from 3.9 to 280 µg/L (ppb).

According to classification provided to the European Chemicals Agency (ECHA), silver dihydrogen citrate (i.e., citric acid and silver citrate EC List No. 460-890-5) is classified as Aquatic Chronic 1 and very toxic to aquatic life with long lasting effects (ECHA 2017).

The environmental assessments also concluded that the remaining components, citric acid (21 CFR 184.1033) and sodium lauryl sulfate (21 CFR 172.822), are of a low order of environmental toxicity and the potential impacts from use of the product in the intended applications are well within safe thresholds.

<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)).

Antimicrobial agents are used in the production and processing of agricultural products due to their effectiveness to kill or inhibit growth of microorganisms in and on foods. This is done to improve food safety for the consumer, as well as to extend the shelf life of food products. There are no known reported positive or adverse effects on human health from use of silver dihydrogen citrate. The high-grade silver and citric acid (used electrolytically to prepare silver dihydrogen citrate) have some potential adverse effects on human health. Citric acid is an irritant of the skin, eyes, and respiratory tract; and chronic exposure to silver and silver salts is most commonly associated with a permanent grey or blue discoloration of the skin (i.e., argyria) and other organs (ATSDR 1990, White et al. 2003, Drake and Hazelwood 2005), but the EPA considers the effect to be a cosmetic and not a toxicologic effect and has approved pesticide registrations on the basis that using the product within safe regulatory levels prevents this effect.

In general, silver has low acute human toxicity. It has been placed in the EPA Toxicity Category III for acute oral and dermal toxicity, but it is not an eye or skin irritant (Toxicity Category IV). Silver is also not a skin sensitizer. Although repeated contact may cause argyria, this is highly unlikely to be a concern at the highly diluted levels used in food facilities. The EPA has summarized its review of the toxicity data for silver and silver compounds as part of a recent re-registration process evaluating the effects on human health from pesticidal use (US EPA 1993). The EPA concluded that no new toxicity studies were required for non-zeolite silver compounds other than a repeat dose inhalation study for silver aerosols. There are also some reports that suggest exposure to high levels of silver salts and other soluble forms of silver may produce other toxic effects, including liver and kidney damage, irritation of the eyes, skin, respiratory, and intestinal tract, and changes in blood cells (Drake and Hazelwood 2005).

The safety of the petitioned substance for use in processing of poultry and produce for human consumption has been evaluated by FDA through FCNs 1768, 1569, and 1600. The product's use in food contact surface sanitization has been evaluated by EPA through the pesticide registration process and through evaluation for the exemption from the requirement of a tolerance of silver in the form of silver dihydrogen citrate. Exposures to silver from the intended use of SDC presents no concern for the safety of human health or the environment, as established by FDA through its review of FCNs 1768, 1569, and 1600. The effective FCNs represent FDA's conclusion that the intended uses of SDC are safe for human health, while FDA's environmental reviews concluded that allowing these FCNs to become effective does not significantly affect the quality of the human environment. A safety assessment for citric acid is not included because FDA has affirmed the substance as generally recognized as safe for direct use in human food under 21 CFR 184.1033.

Evaluation Question #11: Describe any alternative practices that would make the use of the petitioned substance unnecessary (7 U.S.C. § 6518 (m) (6)).

When processing agricultural products, biocides like SDC are paramount in ensuring the safety of consumer. There is no reported literature describing other antimicrobial practices that are available for direct and indirect food contact sanitization in the processing of agricultural products other than the application of biocide solutions. There are other antimicrobial products available for use in organic agricultural processing and sanitization of food contact surfaces: acidified sodium chlorite ($NaClO_2$), chlorine, ozone, and peroxy derivatives (7 CFR 205.605). (See response to Evaluation Question #12.)

Evaluation Question #12: 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)).

Despite information available and government programs efforts to reduce the incidence of *Salmonella*, it continues to be a concern for the meat and poultry industries. Organic acids are excellent antimicrobials against bacteria including *Salmonella* (Mani-López et al. 2012). Organic acids offer several advantages as antimicrobials because they are GRAS, have no limited acceptable daily intake, are low-cost, easy to manipulate, and effect minor sensory changes on the product. For example, an application of 2% acetic acid reduced the incidence of *Salmonella* on pork cheek meat in addition to significantly reducing aerobic plate and coliform counts (Frederick et al. 1994) More than one treatment was found to sometimes help on the bacterial reduction and produces lesser effects on food quality. Also, poultry scald water containing 0.1% acetic acid at 52 C decreased levels of *S.* Typhimurium and *Campylobacter jejuni* (Okrend et al. 1986). However, it is important to use these acids according to good manufacture practices to avoid the development of *Salmonella* strains resistant to acidic conditions.

Lactic acid, produced from fermentation, is currently listed on the National List (7 CFR 205.605(a)) as a non-synthetic material with no restrictions on use and is established as GRAS for using lactic acid as an antimicrobial agent as defined in 21 CFR 170.3(o)(2). The use of lactic acid as an antimicrobial agent is limited to meat products. Lactic acid has been found to be more effective than chlorine treatments of raw meat in poultry processing facilities (Killinger et al. 2010). The acidic nature imparts a mellow and lasting sourness to many products including confectionery.

However, on the NOP National List, there are some synthetic substances allowed, as disinfectants and sanitizers for using on food contact surfaces. These are listed under the 7 CFR 205.605 which delineates the nonagricultural (nonorganic) substances that may be used as ingredients or on processed products that are listed as "organic" or as "made with organic [ingredients or food groups]."

For example, peracetic acid can be substituted for SDC (7 CFR 205.605(b)). Peracetic acid is a mixture of acetic acid and hydrogen peroxide. It is a very strong oxidizing agent and has a strong pungent acetic acid odor. The primary mode of action is oxidation, which differs from SDC. In addition, peracetic acid is considered environmentally safe. Acidified sodium chlorite (using citric acid) and chlorine dioxide, which have the same mode of action as peracetic acid, can also substitute for SDC. (See the NOP petitioned substances database.)

However, bacterial resistance to traditional agricultural biocides is of growing concern (SCENIHR 2010). A number of gram-positive, vegetative bacteria have been isolated from equipment that used chlorine dioxide for high-level disinfection, and several strains, *Bacillus subtilis* and *Micrococcus luteus*, showed stable high-level resistance to the standard use concentration of chlorine dioxide (Martin et al. 2008). The *Bacillus* isolate was also cross-resistant to hydrogen peroxide (7.5%) (Martin et al. 2008). Such reports of bacterial resistance have not been reported for the petitioned substance.

The United States Food and Drug Administration (FDA) regulations allow a number of uses for ethanol in food preparation/storage for humans and animals. For humans, FDA considers ethanol to be "Generally Recognized As Safe" (GRAS) when added directly to human food (21 CFR 184.1293). Ethanol is an approved synthetic substance on the National List for organic livestock production as a disinfectant and sanitizer only (7 CFR 205.603). In addition, ethanol is an approved synthetic substance on the National List for organic crop production when used as an algicide, disinfectant, and sanitizer, including the cleaning of irrigation systems (7 CFR 205.601). Alcohols, including ethanol and isopropanol, are capable of providing rapid broad-spectrum antimicrobial activity against vegetative bacteria, viruses and fungi, but lack activity against bacterial spores (McDonnell and Russell 1999). The antimicrobial action of ethanol is due to rapid denaturation of proteins. A study found that a 7% ethanol solution prevented the growth of four common foodborne microorganisms: Listeria monocytogenes, Salmonella typhimurium, Staphylococcus aureus and Escherichia coli O157:H7 (Ahn et al. 1999), however, the CDC recommends against the use of ethanol or isopropanol as the principal sterilizing agent because these alcohols are insufficiently sporicidal (i.e., spore killing) and cannot penetrate protein-rich materials (CDC 2008). Other shortcomings of ethanol are that it can damage rubber and plastic tubing after prolonged use, is highly flammable and must be stored in cool, well-ventilated areas, and evaporates quickly due to its high volatility, which makes extended exposure time difficult to achieve (CDC 2008)

There are no literature reports to our knowledge that directly compare the efficacy of SDC to that of other organically allowed synthetic substances (e.g., chlorine dioxide, acidified sodium chlorite, ozone, etc.). One important distinction of SDC from these common synthetic substances for disinfection of food and food contact surfaces is the action of the substance. Most of the common synthetic substances are strong oxidizers; thus their antimicrobial efficacy generally increase with oxidation potential (i.e., chlorine dioxide

< acidified sodium chlorite < ozone). The efficacy of SDC arises from it proceeding from a different mechanism of action, interference with cellular processes. In a closely related study, the antimicrobial effects of chlorine (Cl_2), an oxidizer, and Ag^+ ions on bacterial biofilms were compared (Kim et al. 2008). The antimicrobial activities on biofilm cells were investigated by three methods, each of which used a different analytical principle for the determination of antimicrobial activity. The study found that the resistance of the biofilm cells to the oxidant, chlorine, was increased almost 250 times compared with the resistance to the Ag^+ ion. Thus, due to the different mode of action, Ag^+ ions and SDC, in particular, represent a viable alternative for eliminating pathogenic bacteria that demonstrate resistance to common oxidizing antibacterial agents.

<u>Evaluation Information #13:</u> Provide a list of organic agricultural products that could be alternatives for the petitioned substance (7 CFR § 205.600 (b) (1)).

While agricultural and/or natural antimicrobials may be effective in one way, they may be ineffective in another and do not possess broad spectrum antimicrobial properties (Sebranek and Bacus 2007). This stresses the necessity of further research in order to ensure that the food safety of these materials is properly assessed. While current research suggests that natural plant extracts can be effective in controlling pathogens in meat products, the most favorable results tend to result from multiple-barrier food preservation systems, which use combinations of agricultural and/or natural antimicrobials and sodium or potassium lactate (or other synthetic antimicrobial ingredients). However, decreasing the shelf life of a product to accommodate the strict use of natural antimicrobials is another option. A survey of organic agricultural antimicrobials is discussed below.

The USDA Organic Regulations do not permit the addition of nitrite to organic processed meat. Alternative methods like the use of celery powder, which is listed on at 7 CFR Part 205.606 and allowed for use in products labeled as "Organic" only when an organic form is not commercially available, are commonly used in meat products. Trials studying natural antimicrobials for the inhibition of *Listeria monocytogenes* on naturally cured frankfurters have been conducted (Xi et al. 2013). Using celery powder containing 12,000 ppm of nitrite, the concentration of nitrite (when the celery powder was used at 0.4% of the frankfurter formulation) resulted in 48 ppm of nitrite added to the frankfurter mixture. In a conventional curing process, 156 ppm of nitrite is added. The research found that the celery powder achieved the expected color, flavor and other properties of cured meats, but it resulted in lower nitrite levels than occurred with the use of synthetic preservatives.

In the same study by Iowa State University in 2013, powdered concentrates from cranberries, cherries, limes and a blend of cherry, lime and vinegar were evaluated alone and in various combinations for antimicrobial impact on the growth of *L. monocytogenes* in naturally cured frankfurters (Xi et al. 2013). The results showed that cranberry powder at 3% of the formulation, combined with celery powder, achieved inhibition of *L. monocytogenes* following the inoculation of naturally cured frankfurters that was equivalent to that of conventionally cured frankfurters during 49 days of refrigerated storage. Cranberry powder at 1% and 2% in combination with other natural antimicrobials inhibited growth for up to 35 days, while the naturally cured frankfurters without additional antimicrobial ingredients showed growth after 28 days. However, quality assessment of the products showed that 3% cranberry powder was detrimental to the color and sensory and textural attributes of the frankfurters, possibly due to the acidic nature of the cranberry concentrate. It was concluded that, while cranberry concentrate has potential as a natural antimicrobial, it is necessary to develop a means of compensating for the acidic nature of this ingredient to achieve practical applications in organic cured meat products. In addition, for the meat to maintain its organic status, the cranberry powder would also need to be a certified organic ingredient and, per the requirements of 7 CFR 205.606, attempts would need to be made to source organic celery powder.

The effectiveness of essential oils in controlling L. monocytogenes has also been investigated (Campos et al. 2011). The results of the study were promising; however, in many instances, combinations of additives or preservative treatments worked best because the efficacy of the antimicrobials can be influenced by the chemical composition and the physical conditions of various foods. Essential oils (EOs) are oily liquid mixes of volatile and complex compounds that are extracted from different parts of aromatic plants. They are synthesized by plants as secondary metabolites and can be obtained mainly by steam distillation or super critical fluid extraction. Essential oils can contain 20-60 components, depending on the material they come from and the extraction method used. Terpenes and terpenoids make up the constitute majority of the components with the remainder consisting of aromatic and aliphatic compounds of low molecular weight.

Their activity against *Listeria* growth in laboratory media was highly variable (Campos et al. 2011). EOs of bay, coriander, cinnamon, clove, licorice, nutmeg, pepper, oregano, winter savory, spruce and thyme showed the highest inhibitory activity. The effectiveness of oils of basil, lemon balm, marjoram, mastic tree, rosemary and sage were lower than those mentioned above, whereas Listeria showed high resistance to EOs of aniseed, caraway, fennel, garlic, ginger, onion and parsley.

According to the research, the antimicrobial activity of EOs is largely dependent on their composition; however, the mechanism of antimicrobial action of EOs is not well understood. Inhibitory actions are mostly related to the identity of the majority terpenes and terpenoid components, but the minor components have a strong influence on the effectiveness of their antimicrobial action. The main components often consist of: carvacrol, thymol, linalool, eugenol, trans-cinnamaldehyde, p-cymene, 1,8-cineole (eucalyptol) and γ-terpinene, and the research suggests that several components of EOs are involved in the fixation on cell walls and cellular distribution. It's reported that EO components may degrade the cell wall, damage the cytoplasmic membrane and proteins of the membrane, leak vital intracellular compounds, coagulate cytoplasm and deplete the proton motive force, and that EOs also interact with one another, potentially leading to synergistic antimicrobial effects between various oils (Campos et al. 2011). For example, the growth of *L. monocytogenes* was suppressed in laboratory media more when a combination of oils was used (oils of oregano and rosemary; oils of basil, rosemary or sage; and oils of rosemary and licorice) than when these oils were used alone.

Further results in various samples suggested that EOs have lower activity in foods with high fat content. This may be due to: (i) EO dissolution in the lipid fraction of the food, decreasing the concentration in the aqueous phase, together with antimicrobial action; (ii) the reduced water content in foods, particularly in fatty foods, in relation to culture media, which may slow down the movement of the preservative to the active site in the microbial cell; and (iii) the presence of fat in the food which may produce a protective layer around the bacteria (Campos et al. 2011).

Storage temperature, pH, physical structure of food, fat, protein, sugar content, and sensory properties all need to be considered when deciding whether EOs will be affective for controlling pathogens. It was reported that chicken frankfurters treated with 2%v/w of clove oil were unacceptable to the consumer, whereas samples with 1% were accepted. The latter level had effective antilisterial activity in the food. It was found that combining EOs would allow the use of lower levels to reduce Listeria growth, minimizing the unacceptable sensory changes in the food. Indirect uses of EOs, for example in water to wash vegetables similar to the use of chlorine, or in the impregnation of porous surface of wood in cheese ripening to improve sanitary safety, are also being considered.

Report Authorship

The following individuals were involved in research, data collection, writing, and editing of this report:

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All individuals are in compliance with Federal Acquisition Regulations (FAR) Subpart 3.11—Preventing Personal Conflicts of Interest for Contractor Employees Performing Acquisition Functions.

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