Petition to the National Organic Program to Add

Silver Dihydrogen Citrate

to the National List of Allowed and Prohibited Substances

Petitioner
Pure Bioscience, Inc.
1725 Gillespie Way
El Cajon, CA 92020

Agent
Mitchell A. Cheeseman, Ph.D.
Steptoe & Johnson, LLP
1330 Connecticut Avenue NW
Washington, DC 20036

Item A.1 *Indicate the National List Section to Which the Petitioned Substance Will Be Added/Removed*	Pure Bioscience, Inc. is petitioning to add silver dihydrogen citrate to the National List as a nonagricultural (nonorganic) substance allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients)" pursuant to 7 C.F.R. § 205.605(b).
Item B.1. *Substance Name*	Silver dihydrogen citrate
Item B.2. *Petitioner and Manufacturer Information*	<u>Petitioner and Manufacturer</u> Pure Bioscience, Inc. 1725 Gillespie Way El Cajon, CA 92020 <u>Manufacturer Contact</u> Dolana Blount, Vice President of Regulatory Affairs 619-596-8600 ext. 105 dblount@purebio.com <u>Agent for the Petition</u> Dr. Mitchell Cheeseman Steptoe & Johnson, LLP 1330 Connecticut Avenue NW Washington, DC 20036 202-429-6473 mcheeseman@steptoe.com
Item B.3. *Intended or Current Use*	The substance is intended for use as: (1) An antimicrobial processing aid in the processing of: (a) Poultry carcasses, parts, and organs; and (b) Fruits and vegetables, except the substance is not for use on citrus fruit or grapes intended for winemaking. (2) A disinfectant and sanitizer for food contact surfaces and food processing equipment.
Item B.4. *Intended Activities and Application Rate*	When used as an antimicrobial for food processing, the substance is an aqueous solution of silver dihydrogen citrate and is further diluted on site to achieve a target concentration of the active antimicrobial component. The target concentrations (i.e., application rate) and method of application are as follows: (1) Poultry carcasses, parts, and organs: 30 ppm silver as silver dihydrogen citrate, application by spray or dip only (chiller baths are not permitted) (2) Fruits and vegetables: 30 ppm, application by spray or dip. The substance is not for use on citrus fruit or grapes intended for winemaking. The substance may not be used in combination with any other silver-containing antimicrobial.

	When used for disinfection and sanitization of previously cleaned food contact surfaces and equipment, the substance is a ready-to-use aqueous solution of silver dihydrogen citrate formulated to provide 30 ppm silver as silver dihydrogen citrate. Unlike other hard surface sanitizers, silver dihydrogen citrate meets the efficacy performance standards for disinfection and sanitization at the same 30 ppm use level for the ready-to-use product.
Item B.5. *Manufacturing Process*	Silver dihydrogen citrate is produced electrolytically, through the immersion of silver electrodes in an aqueous solution of anhydrous 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 solution is stabilized with sodium lauryl sulfate.
Item B.6. *Ancillary Substances*	Citric acid: this substance is a component of the solution and is used as a stabilizer and pH control agent. Sodium lauryl sulfate: this substance is intentionally added during manufacturing to act as a stabilizer for the solution.
Item B.7. *Previous Reviews*	Silver dihydrogen citrate has been certified Kosher Pareve by Kosher Supervision of America.[1]
Item B.8. *Regulatory Authority*	The substance has been reviewed and approved by the Food and Drug Administration for use as a food contact substance in the applications identified above in Item B.3. and B.4., resulting in effective Food Contact Notifications 1569 (poultry use)[2] and 1600 (fruit and vegetable use).[3] The substance has been reviewed and approved by the Environmental Protection Agency for use as an antimicrobial, disinfectant, fungicide, and virucide, food contact surface sanitizer as identified above in Item B.3. and B.4. 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.[4] The substance has been reviewed and approved by the U.S. Department of Agriculture Food Safety and Inspection Service for addition to

[1] Certificate included as Appendix 1.
[2] http://www.accessdata.fda.gov/scripts/fdcc/?set=FCN&id=1569. A copy of the Inventory Listing is included as Appendix 2.
[3] http://www.accessdata.fda.gov/scripts/fdcc/?set=FCN&id=1600. A copy of the Inventory Listing is included as Appendix 2.
[4] 74 Fed. Reg. 27447 (June 10, 2009). A copy is included with Appendix 2.

	Directive 7120.1, the List of Safe and Suitable Ingredients Used in the Production of Meat, Poultry, and Egg Products.[5] The substance 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."[6]
Item B.9. *Chemical Abstracts Service (CAS) Number and Product Labels*	No CAS number has been assigned or sought for the substance. EPA approved product labels for the registrations identified above are included. Also included are the Safety Data Sheet (SDS) for the concentrate and ready-to-use products and release specifications for each (Appendix 3.
Item B.10. *Physical and Chemical Properties*[7]	Appearance: Clear, colorless liquid Odor: Practically odorless pH: 1.45 (as a concentrated solution); 2.0 (Ready to use food contact surface sanitizing solution) Specific gravity: 1.091 (concentrated solution); 1.00 (Ready to use solution) Solubility: water soluble
Item B.10(a) *Chemical interactions with other substances, especially substances used in organic production*	SDC is incompatible with aluminum sulfate, aluminum ammonium chloride, aluminum orthophosphate, chlorides, sequestering agents designed to remove transition metals from solution, EDTA (above 1.5%), and calcium hardness above 300 ppm. These substances are not on the National List. The product is compatible with most metals including stainless steels. Ionic silver rapidly reacts with chlorides and some other anions that will result in low solubility silver salts. This reaction would potentially affect stability of the product. We recognize that two chloride salts, calcium and potassium, are permitted for use in organic processing, but the chloride salts are not expected to be used during the early processing stages. Therefore, the silver dihydrogen citrate would not be anticipated to have the opportunity to react with those substances and adversely impact the stability of the product.
Item B.10.(b) *Toxicity and environmental*	The substances of environmental toxicological concern resulting from the use of the product are silver (CAS Reg. No. 7440-22-4), citric acid

[5] See the entry for FCN 1569, https://www.fsis.usda.gov/wps/wcm/connect/bab10e09-aefa-483b-8be8-809a1f051d4c/7120.1.pdf?MOD=AJPERES. A copy of the No Objection Letter also is included as Appendix 2.
[6] A copy of the NSF letter is included with Appendix 2.
[7] These are the physical and chemical properties for the silver dihydrogen citrate concentrated solution, except as noted.

persistence	(CAS Reg. No. 64-19-7), and sodium lauryl sulfate (SLS) (CAS Reg. No. 79-21-0). Notably, citric acid already is listed on the National List under 7 C.F.R. § 205.605. The environmental toxicity of citric acid has been reviewed as part of the OECD's High Production Volume program and a SIDS Initial Assessment Report is available (included as Appendix 4).[8] This review concludes that "citric acid is not judged to be a substance that presents a hazard to the environment." Citric acid also has been the subject of a HERA review, which concluded that it has "a very favourable ecological profile" and that "[d]ue to the very low aquatic toxicity and the ready biodegradability, wide dispersive use of citric acid does not present a hazard to the environment."[9] Sodium lauryl sulfate has been reviewed as part of the OECD HPV program and a SIDS Initial Assessment Report is available (included as Appendix 5),[10] which concluded that the chemical "can be considered to present a low potential for risk to man and the environment." Silver is the subject of an environmental review under EPA's pesticide registration program and currently is undergoing reregistration review by EPA. The environmental fate and ecotoxicity data available to EPA are summarized in the registration scoping document (included as Appendix 6). The environmental impacts of the product for the food processing intended uses under the NOP have been reviewed by FDA and considered to be of no significant impact. In addition, EPA has reviewed the environmental impacts as part of its registration process for use of the silver dihydrogen citrate as a disinfectant and sanitizer for food contact surfaces and processing equipment.
Item B.10(c) *Environmental impacts from its use and/or manufacture*	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. The environmental assessments submitted to FDA for the poultry and produce applications, with FDA's Findings of No Significant Impact (FONSI) are included with this submission as Appendix 7. As discussed in these EAs, both citric acid and SLS are of a low order of environmental toxicity and the potential impacts from use of the product in the intended applications is well within safe thresholds. Similarly, the

[8] OECD SIDS Initial Assessment Report, Citric Acid, January 2001, http://webnet.oecd.org/Hpv/UI/handler.axd?id=ff78c453-36c1-430d-9034-63e15899d24b.

[9] Human and Environmental Risk Assessment on ingredients of Household Cleaning Products*, Citric Acid and Salts (CAS# 77-92-9; 5949-29-1; 6132-04-3)*, April 2005, also included with Appendix 4.

[10] OECD SIDS Initial Assessment Report, Sodium dodecyl sulphate, January 2001.

	potential environmental exposure to silver is within safe thresholds. As part of EPA's reregistration review, while the agency noted that some additional environmental fate studies are required, it concluded that EPA has an adequate ecological toxicity database for silver and silver salts in order to address ecological risk from the various uses of these products.[11]
Item B.10 (d) *Effects on human health*	The safety of the product for use in processing of poultry and produce for human consumption has been evaluated by FDA through Food Contact Notifications (FCN) 1569 and 1600. The safety assessments submitted to FDA are included in Appendix 8. 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 C.F.R. § 184.1033. The safety of the product for 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. Silver was first registered as a pesticide in the United States in 1960.[12] Silver has been registered for a variety of antimicrobial applications and use sites, including medical premises and equipment, human drinking water systems, materials preservatives, swimming pool algaecides, drinking water filters, fibers, textiles, spas, hot tubs, and whirlpools.[13] Silver and silver compounds are currently in the on-going pesticide re-registration process, through which the EPA evaluates the effects on human health from pesticidal uses of silver. EPA has summarized its review of the toxicity data as part of that re-registration process,[14] and concluded that no new toxicity studies were required for non-zeolite silver compounds other than a repeat dose inhalation study for silver aerosols.[15] As discussed in that review, silver is known to cause argyria, a permanent discoloration of the skin and/or eyes, but EPA considers the effect to be a cosmetic and not toxicologic effect and has approved pesticide registrations on the basis of safe regulatory levels established based on this effect.[16]
Item B.10 (e) *Effects on soil organisms, crops,*	As the approval sought is not for use in crop or livestock production, there are no anticipated effects on soil organisms, crops, or livestock.

[11] US EPA, Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for Silver, Silver Salts, Silver Zeolites (Copper and Zinc) and Silver Sodium Hydrogen Zirconium Phosphate For Registration Review (June 2009), p. 11-12.
[12] Id. , p. 5.
[13] Id.
[14] US EPA, Silver, Silver salts, and Silver Zeolites: Human Health Assessment Scoping Document in Support of Registration Review (June 2009), starting p. 9, included with this submission as Appendix 9.
[15] Id., p. 2.
[16] Id., p. 22.

or livestock	Any effects on the environment are addressed Items B.10(b)-(c).
Item B.11 *Safety Information*	The Safety Data Sheet for the product is provided in Appendix 3. There is no substance report on silver available from the National Institute of Environmental Health Studies (NIEHS). There is a report from the National Toxicology Program on nanosilver, which includes information on silver ion. The product does not contain nanosilver, so the nomination report is not applicable. As the sections on chemical properties and toxicity effects relate to silver generally, as well as nanosilver specifically, they are included here as Appendix 10.
Item B.12 *Research Information*	The following information is included as Appendix 11: (1) NIOSH RTECS summary on silver; (2) EPA IRIS summary on silver; (3) NLM Hazardous Substances Data Bank summary; (4) ATSDR Toxicological Profile; (4) A Scientific Opinion by the European Food Safety Authority on the use of silver as a food additive. No information presenting the position that silver dihydrogen citrate should not be permitted in the handling of an organic product has been located.
Item B.13 *Petition Justification Statement*	Silver dihydrogen citrate (SDC) is a safe and effective antimicrobial for use in the processing of food to reduce populations of microorganisms that cause foodborne illnesses, resulting in safer food for consumers. Food safety is an on-going concern for regulatory agencies and consumers. Outbreaks of foodborne illnesses continue to cause significant adverse impacts on human health and the economy. FDA, through the Food Safety Modernization Act (FSMA), is particularly focused on ensuring that food manufacturers and processors have the tools available to successfully implement preventive controls and ensure the safety of the food introduced into commerce. As part of its food safety measures, industry continues to seek effective antimicrobial products that can be used without harm to consumers, workers, or the environment. SDC meets all of these requirements. Pure Bioscience has undertaken efficacy studies through the Food Science Institute (FSI) at Kansas State University for the food processing applications. In poultry processing, the FSI study demonstrates that SDC reduces the *Salmonella* load under typical use conditions by an average of over two logs compared to a deionized water control. To model typical industry practice, spray application with the SDC was followed with immersion of the poultry samples in a chiller incorporating 50 ppm of chlorine. The combined treatment resulted in near complete elimination of *Salmonella* on the poultry. Similarly, in an efficacy study on fruits and vegetables, spray application of SDC followed by a 20 ppm chlorine rinse reduced microbial load of *Salmonella*, *E. coli* and *Listeria*

	by 2-3 logs compared to deionized water control. Concurrently with the efficacy studies, FSI conducted studies examining the impact of treatment on the nutritional and sensory qualities of the poultry and produce, and established that treatment with SDC has no significant impact on these properties. Poultry and produce treated with SDC does not show the discoloration often seen with many of the chemicals currently allowed under the NOP regulations and the overall yield on poultry is not impacted. In addition, the studies showed that treated and untreated poultry undergo similar increases in aerobic plate count when held up to 7 days, demonstrating that SDC treatment does not prolong shelf-life. Pure Bioscience also has conducted efficacy testing for the hard surface disinfectant and sanitizing uses. Testing was conducted according to EPA guidelines for efficacy at that time, specifically DIS/TSS-4, "Sanitizing rinses (for previously cleaned food-contact surfaces)" and DIS/TSS-2, "Supplemental Recommendations." Under the conditions of this testing, the product demonstrated a >99.999% reduction of *Staphylococcus aureus* and *E. coli* after a 30 second exposure period. Further efficacy testing has permitted the addition of claims to the EPA labels for use of the product against many other organisms, as can be seen in Appendix 3. Because sanitization and disinfection can be achieved for the ready-to-use product at 30 ppm, facilities get additional protection with one product and without needing to dilute the product to varying levels to obtain the desired level of antimicrobial action. Many of the chemistries currently allowed under the NOP require significantly higher than allowed concentrations to meet disinfection criteria. The allowed concentrations also are not sufficient to adequately control organisms such as Norovirus, a growing food safety concern. Furthermore, as a ready-to-use product, the potential for user error in over- or under-dosing the sanitizer is eliminated, as is worker exposure to concentrated chemicals that present higher health risks when stored at facilities and introduced into the production process. SDC has long-term benefits for use in facilities because it is non-caustic and very stable. The non-corrosive and non-caustic solution helps to maintain the integrity of processing equipment. Reducing equipment damage is fiscally beneficial for processors and helps ensure better environmental sanitation. Equipment corrosion is a major complaint for many of the chemicals currently allowed on the NOP. This corrosion can lead to microbial harborage areas and increase the potential threat of contamination of foods from the environment. The stability of the product, which has been shown to have a shelf-life of several years, means that the product can be stored in a facility for a long period of time without a reduction in efficacy upon use. SDC also provides benefits to facility workers and USDA inspectors, as it

	does not produce fumes and is practically odorless. Although repeated contact may cause some body tissues to discolor, in a condition called argyria, this is highly unlikely to be a concern at the levels used in food facilities. Finally, 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 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. There are other antimicrobial products available for use in organic handling: acidified sodium chlorite; chlorine; and peracetic acid. SDC would be an alternative to these products and provides significant benefits in terms of human and environmental safety, and ease and safety of use in food facilities. Many of these chemicals have been associated with respiratory and eye illnesses for workers exposed during processing.[17] Strong oxidizing chemicals are also highly corrosive to equipment. The unstable nature of several of the chemistries when diluted can lead to ineffective use. Heightened industry and regulatory attention to the safety and efficacy of chemicals used in processing food and plant sanitation is driving the need for safer, stable, and highly effective chemistries such as silver dihydrogen citrate.

[17] See, e.g., https://www.cdc.gov/niosh/topics/poultry/evaluating.html, http://scienceblogs.com/thepumphandle/2016/12/13/poultry-workers-suffer-while-industry-uses-chemicals-to-disinfect-your-chicken/.

Attachment 1

KOSHER SUPERVISION OF AMERICA

בס"ד

Sep 15, 2016

The following product(s) prepared by the named company are certified kosher with the stated requirements:

Pure BioScience, Inc.
(P-0034)

1725 Gillespie Way
El Cajon CA 92020
USA

Brand	Product Name	UKD-ID	D/P/M	Symbol Required	Special Conditions
Pure	Axenohl®	KSAV3-A4X2F60	P	KSA	
Pure	PURE® CONTROL Direct Food Contact Concentrate	KSAV3-W6D2B81	P	KSA	
Pure	PURE® CONTROL Direct Food Contact Ready-To-Use	KSAV3-J1X2G43	P	KSA	
Pure	PURE® CONTROL Direct Food Contact Use-Dilution	KSAV3-S0E4X92	P	KSA	
Pure	PURE® Hard Surface	KSAV3-C4S8V38	P	KSA	
Pure	PURE® Multi-Purpose & Floor Cleaner Concentrate	KSAV3-M2E3U28	P	KSA	
Pure	PURE® Multi-Purpose Hi-Foam Cleaner Concentrate	KSAV3-I3F6F44	P	KSA	
Pure	Silver Dihydrogen Citrate 2400	KSAV3-X4Y7X53	P	KSA	
Pure	Silver Dihydrogen Citrate 2500	KSAV3-S8C4G21	P	KSA	
Pure	SILVÉRION® 2400	KSAV3-Y7G2I22	P	KSA	

This certificate expires on
Aug 31, 2017

Rabbi Binyomin Lisbon
Kashrus Administrator

P.O.Box 35721, Los Angeles, Ca 90035 - (310) 282-0444 - Fax (310) 282-0505 - Email info@ksakosher.com - www.ksakosher.com

Attachment 2

This rule is not a ''major rule'' as defined by 5 U.S.C. 804(2).

Under section 307(b)(1) of the Clean Air Act, petitions for judicial review of this action must be filed in the United States Court of Appeals for the appropriate circuit within 60 days from the effective date of this rule. Filing a petition for reconsideration by the Administrator of this final rule does not affect the finality of this rule for the purposes of judicial review nor does it extend the time within which a petition for judicial review may be filed, and shall not postpone the effectiveness of such rule or action. This rule may not be challenged later in proceedings to enforce its requirements. (*See* section 307(b)(2).)

List of Subjects in 40 CFR Part 62

Environmental protection; Administrative practice and procedure; Air pollution control; Intergovernmental relations; Reporting and recordkeeping requirements.

Dated: April 10, 2009.

Beverly H. Banister,

Acting, Regional Administrator, Region 4.

■ 40 CFR part 62, subpart RR, is amended as follows:

PART 62—[AMENDED]

■ 1. The authority citation for Part 62 continues to read as follows:

Authority: 42 U.S.C. 7401 *et seq.*

Subpart RR—Tennessee

■ 2. Section 62.10626 is amended by adding paragraphs (b)(6) and (c)(3) to read as follows:

§ 62.10626 Identification of plan.

* * * * *

(b) * * *

(6) City of Memphis Implementation Plan: Federal Emission Guidelines Hospital/Medical/Infectious Waste Incinerators (HMIWI), submitted on February 16, 2006, by the Memphis and Shelby County Health Department.

(c) * * *

(3) Existing Hospital/Medical/Infectious Waste Incinerators

■ 3. Part 62 is amended by adding a new undesignated center heading to subpart RR and a new § 62.10632 to read as follows:

Air Emissions From Existing Hospital/Medical/Infectious Waste Incinerators (HMIWI)—Section 111(d)/129 Plan

§ 62.10632 Identification of sources.

The Plan applies to all existing HMWI facilities at St. Jude Children's Hospital in the City of Memphis, for which construction was commenced on or before June 20, 1996.

[FR Doc. E9–13595 Filed 6–9–09; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA–HQ–OPP–2007–0395; FRL–8412–1]

Residues of Silver in Foods from Food Contact Surface Sanitizing Solutions; Exemption from the Requirement of a Tolerance

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: This regulation amends the exemption from the requirement of a tolerance for residues of silver (excludes silver salts) in or on all foods when applied or used in public eating places, dairy processing equipment, and food-processing equipment. ETO H2O, Inc., submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act requesting to establish concentration limits for silver in end-use solutions eligible for tolerance exemption. The regulation being established will exempt all foods from the requirement of a tolerance for residues of silver resulting from contact with surfaces treated with solutions in which the end-use concentration of silver is not to exceed 50 parts per million (ppm).

DATES: This regulation is effective June 10, 2009. Objections and requests for hearings must be received on or before August 10, 2009 and must be filed in accordance with the itructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA–HQ–OPP–2007–0395. To access the electronic docket, go to *http://www.regulations.gov*, select ''Advanced Search,'' then ''Docket Search.'' Insert the docket ID number where indicated and select the ''Submit'' button. Follow the instructions on the regulations.gov web site to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at *http://www.regulations.gov*, or, if only available in hard copy, at the Office of Pesticide Programs (OPP) Regulatory Public Docket in Rm. S–4400, One Potomac Yard (South Building), 2777 S. Crystal Drive Arlington, VA. The hours of operation of this Docket Facility are from 8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays. The Docket telephone number is (703) 305–5805.

FOR FURTHER INFORMATION CONTACT: Marshall Swindell, Antimicrobials Division (7510P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460–0001; telephone number: (703) 308–6341; e-mail address: *swindell.marshal@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

You may be potentially affected by this action if you are a dairy cattle milk producer, food manufacturer, or beverage manufacturer. Potentially affected entities may include, but are not limited to:

- Food Manufacturing (NAICS code 311).
- Beverage Manufacturing (NAICS code 3121).
- Dairy Cattle Milk Production (NAICS code 11212).

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The North American Industrial Classification System (NAICS) codes have been provided to assist you and others in determining whether this action might apply to certain entities. To determine whether you or your business may be affected by this action, you should carefully examine the applicability provisions in 40 CFR 180.940 (a) Tolerance exemptions for active and inert ingredients for use in antimicrobial formulations (Food-contact surface sanitizing solutions). If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Access Electronic Copies of this Document?

In addition to accessing an electronic copy of this **Federal Register** document through the electronic docket at *http://*

www.regulations.gov, you may access this **Federal Register** document electronically through the EPA Internet under the ''**Federal Register**'' listings at *http://www.epa.gov/fedrgstr*. You may also access a frequently updated electronic version of 40 CFR part 180 through the Government Printing Office's pilot e-CFR site at *http://www.gpoaccess.gov/ecfr*.

C. Can I File an Objection or Hearing Request?

Under section 408(g) of the FFDCA, as amended by the FQPA, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. The EPA procedural regulations which govern the submission of objections and requests for hearings appear in 40 CFR part 178. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA–HQ–OPP–2007–0395 in the subject line on the first page of your submission. All requests must be in writing, and must be mailed or delivered to the Hearing Clerk on or before August 10, 2009.

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing that does not contain any CBI for inclusion in the public docket that is described in **ADDRESSES**. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit your copies, identified by docket ID number EPA–HQ–OPP–2007–0395, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

- Mail: Office of Pesticide Programs (OPP) Regulatory Public Docket (7502P), Environmental Protection Agency, 1200 Pennsylvania Ave., NW.,Washington, DC 20460–0001.

- Delivery: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S–4400, One Potomac Yard (South Building), 2777 S. Crystal Drive, Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The docket telephone number is (703) 305–5805.

II. Background and Statutory Findings

In the **Federal Register** of July 11, 2007 (72 FR 37779) (FRL–8136–1), EPA issued a notice pursuant to section 408(d)(3) of the FFDCA, 21 U.S.C. 346a(d)(3), announcing the filing of an pesticide tolerance petition (PP 7F7178) by ETO H20, Inc, 1725 Gillespie Way, El Cajon, CA 92020. The petition requested that 40 CFR 180.940(a) be amended by establishing concentration limits for Silver in end-use solutions eligible for the tolerance exemption in all foods from treatment of food contact surfaces in public eating establishments, dairy processing equipment, and food processing equipment and utensils not to exceed silver at 50 ppm. The notice referenced a summary of the petition prepared by ETO H20, Inc., 90 Boroline Rd Allendale, NJ 07401, the registrant, which is available to the public in the docket at *www.regulations.gov*, Docket ID Number EPA–HQ–OPP–2007–0395. There were no comments received in response to the notice of filing.

In drafting the regulatory language for this exemption, EPA has adopted more restrictive language than suggested in the petition to ensure that the scope of the exemption does not exceed the form of silver evaluated in the risk assessment supporting this action. As revised, the tolerance expression would now read:

> Silver ions resulting from the use of electrolytically-generated silver ions stabilized in citric acid as silver dihydrogen citrate (does not include metallic silver).

This revised tolerance expression excludes any other silver-containing compounds whether they are other silver salts, complexes with inorganic polymers such as zeolites, or metallic silver in any form or dimension including nanoscale.

EPA understands that this petition was not intended to extend to silver salts accordingly EPA has modified the regulatory language to make this clear.

Section 408(c)(2)(A)(i) of the FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is ''safe.'' Section 408(c)(2)(A)(ii) defines ''safe'' to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.'' This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Pursuant to section 408(c)(2)(B), in establishing or maintaining in effect an exemption from the requirement of a tolerance, EPA must take into account the factors set forth in section 408(b)(2)(C), which requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to ''ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....''

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. First, EPA determines the toxicity of pesticides. Second, EPA examines exposure to the pesticide through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings.

III. Toxicological Profile

A. Toxic Effects

Consistent with section 408(b)(2)(D) of FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action and considered its validity, completeness and reliability and the relationship of this information to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. The nature of the toxic effects caused by silver are discussed in this unit.

Silver ions and preparations containing silver in an ionic state have been used for over a century for medicinal and bactericidal purposes. Because of its bactericidal properties, silver has been used as a topical treatment for burns, as a treatment for venereal diseases, as an ingredient in cosmetic formulations and in the sanitation of swimming pools and hot tubs/spas. Silver has also been used in dentistry (as amalgams and as an ingredient in mouth washes), in acupuncture, jewelry making, and photography. Silver can be found in electroplating as well as in paints and in water purification systems.

The toxicity of silver is well understood based on epidemiological data from humans, toxicology data in animals, and documented information on the metabolism of silver in mammalian species. Unlike for other pesticides, EPA does not have a conventional check-list of guideline laboratory animal studies to assess human risk from exposure to silver. Based on the extensive past uses of

silver and EPA's knowledge and experience about those uses of the compound, however, it is apparent that humans and laboratory animals do not handle elevated doses of silver in the same manner. For this reason, additional conventional laboratory animal toxicity studies would not provide a better understanding of the effects of silver in humans. Further, the Agency has determined that silver and several of its salts (chloride, sulfate nitrate and acetate) can be reviewed together because these silver salts react similarly in aqueous media and the major active ion is the silver ion.

A human biomonitoring study conducted in 1935, as reported in the *Journal of the American Medical Association* by L.E. Gaul and H.E. Staud, has served as the basis for establishing regulatory limits for silver in drinking water and in the diet. The results from this study were further supported by the results from an inhalation study conducted by Pillsbury and Hill in 1939, which established inhalation limits for silver in humans. In both studies, the effect of concern was argyria, a bluish discoloration of the skin. Argyria, while a permanent condition, is a cosmetic condition. The function of the skin as an organ is not compromised and the resulting discoloration is not associated with systemic toxicity. In the 1935 study by Gaul and Staud, silver was administered for medicinal purposes to 70 patients for periods from 2 to 9 years. Of the 70 patients receiving medicinal silver, 1/70 developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 0.014 milligram/kilogram/day (mg/kg/day) and was considered a lowest observed effect level. Other patients did not develop argyria until doses five times higher were administered. This study and an inhalation biomonitoring study by Pillsbury, *et al*, clearly determined the endpoint of concern for humans. Interestingly, the skin form of argyria has not been reported in laboratory animals when doses that are approximately 4 orders of magnitude higher (100 mg/kg) are administered.

Further support for not requiring additional laboratory animal studies for silver is provided from the results of the developmental toxicity study in rats, conducted by the National Toxicology Program (NTP). In a developmental study conducted in 2002, silver acetate was administered by gavage on days 6 – 19 of gestation. No developmental effects were reported at doses up to 100 mg/kg; maternal animals were observed to have piloerection and rooting behavior at 30 mg/kg. The observed effects in maternal animals would not be expected to occur in humans and are frequently observed in animal studies. These observations, when made in the absence of other clinical findings are not considered adverse when establishing a ''no adverse effect level.'' More importantly, the results from this study did not demonstrate an increased susceptibility of offspring, nor did it demonstrate systemic toxicity. This study corroborates the use of the information provided by the human biomonitoring study in determining dietary limits for silver and further supports our decision to not rely on animal data when assessing the health effects of silver in humans.

In addition to the information gleaned from the biomonitoring studies and the developmental toxicity study, the reviews of the literature by other EPA offices and national and inter-national organizations provide supplemental support that argyria is the primary effect in humans (e.g. EPA's Integrated Risk Management System, Agency for Toxic Substances and Disease Registry, the World Health Organization). Also the acute oral toxicity studies that have been provided to support the registration of silver as an antimicrobial agent establish LD_{50s} between 2,000 and 5,000 mg/kg. These values are above the limit dose for acute toxicity. For other silver salts, such as silver cyanide, the LD_{50} values may be significantly lower based on the molecules to which the silver ions are attached. For the antimicrobial silver covered by this exemption, the LD_{50} ranges are very high because the silver ions have very low acute toxicity.

Finally, the pharmacokinetics of silver is understood and may explain the low systemic toxicity potential of the compound. Pharmacokinetics describes what the body does to a chemical when it is introduced into the body including how it is metabolized, distributed, and eliminated. When silver is introduced into the body by the oral or dietary route, it is absorbed by the digestive system and then enters the liver before it reaches the rest of the body (referred to as first-pass metabolism). This first pass through the liver greatly reduces the bioavailability of silver in that about 90% of the orally administered dose is eliminated in the feces. The remaining 10% that is not eliminated in the feces, reacts with proteins by binding to a specific chemical group contained in the structure of the protein. By forming silver-protein complexes through this binding action, the remaining silver is removed from circulation. This remaining fraction accounts for the background levels of silver that are found within the body. At excessive doses, the pathways of elimination become saturated and deposition of these complexes in the tissues is increased. The formation of these complexes and deposition in the skin, mucous membranes, and conjunctiva is the primary mechanism which results in the development of argyria. Based on information from biomonitoring studies, the lowest observed effect level for the formation of argyria was 1 gram (total dose), which was converted to an oral dose of 0.014 mg/kg/day.

B. Regulatory Levels

Safe exposure levels for silver have been established by several regulatory Agencies including the Food and Drug Administration, Occupational Safety and Health Administration and other offices within EPA based on the common endpoint argyria and using the same human studies. Argyria is a blue-gray discoloration of the skin and is not considered as being of toxicological concern. Argyria is cosmetically disfiguring and permanent in nature; however, the occurrence of this condition does not adversely affect organ function or threaten human health. EPA believes that by regulating for argyria, it is protecting the public from this permanent cosmetic effect as well as any potential toxic manifestations of silver that may occur at much higher doses. There is no animal condition that would mimic the dermatologic form of argyria found in humans following exposure to silver by various routes. This may be due in part to the protection imparted by the presence of the fur or by the fact that laboratory animal species are not routinely exposed to direct sunlight. Argyrosis, a form of argyria which involves silver deposition in organs, has been documented. In laboratory species, the effects of silver toxicity have been reported to involve pathology to the liver (necrosis) and kidney (thickening of the basement membranes of the glomeruli), and, at elevated levels, death.

The effect on which silver is regulated (argyria) occurs only after chronic exposure. Both the Secondary Maximum Contamination Level (SMCL) reported by the EPA's Office of Water and the oral reference dose (RfD) reported under the EPA's Integrated Risk Information System (IRIS) were determined based on the previously-mentioned human biomonitoring by Gaul and Staud. For the SMCL, additional mathematical derivations were applied to the oral equivalent dose

to the study Lowest Observed Adverse Effect Level (LOAEL) of 0.014 mg/kg/day to obtain a 0.1 milligram/Liter (mg/L) dose level. The factors applied for changing volume to mass account for the slight difference in the values reported for the SMCL (0.003 mg/kg/day) and for the RfD (0.005 mg/kg/day).

In deriving the chronic dietary regulatory level (RfD) and the SMCL, a safety factor of 3X was applied based on the following rationale as reported by the Office of Water and IRIS. First, the critical effect was cosmetic and not of toxicological significance. Second, the derivation of the LOAEL included the most sensitive individual since other patients did not present with argyria unless dose levels five times higher were administered. Finally, in the human biomonitoring study, silver was administered to these individuals over a period of time that is in excess of chronic exposure and that approaches a level that would be considered a life time exposure duration. Therefore, the dose that was administered was determined as being one that would mimic lifetime exposure.

For the oral exposure route, the Agency is relying on the drinking water Secondary Maximum Contaminant Level (SMCL) of 0.1 mg/L (0.003 mg/kg/day) based on skin discoloration and graying of the whites of eyes (argyria). The Agency applied an additional 3X uncertainty factor to further address the lack of a NOAEL in the study on which this assessment and all regulatory advisories are set. This additional 3X factor was not imposed due to the lack or need for additional standard animal toxicity testing. Thus, a composite database factor of 10X is being applied to account for a lack of NOAEL in the Gaul and Staud (1935) study. This composite factor of 10 should be sufficient for providing protection from the non-toxic effects which may result from chronic oral exposure to silver.

Chronic Dietary Reference Dose (RFD) = 0.003 mg/kg/day ÷ 3 = 0.001 mg/kg/day

Alternatively, a roughly equivalent chronic RfD can be derived by dividing the oral equivalent dose from the Gaul and Staud study (0.014 mg/kg/day) by a factor of 10X.

Following dermal exposure, silver ions tend to bind to the skin and do not penetrate the skin to cause systemic effects. Rather, skin discoloration is the only effect induced by silver exposure through the dermal route. Although this discoloration appears to be the same effect that results from oral and inhalation exposure, the mechanism by which discoloration occurs following dermal exposure is not the same as the mechanism leading to argyria following other routes of exposure. Systemic uptake and distribution of silver following dermal exposure does not occur, and the discoloration is the result of a localized reaction. Again, the effect is not adverse and there is no reason to believe that there would be an increase in susceptibility based on age to the nontoxic discoloration. Susceptibility to this cosmetic event is a function of dose and not age.

IV. Aggregate Exposures

To establish a tolerance, it must be shown ''that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information.'' Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

Silver is commonly used for a variety of non-pesticidal industrial uses, which include but are not limited to photography, cosmetics, sunscreens, manufacture of inks and dyes, mirror production, and in jewelry. These sources result in primary exposures being via the dermal route. As previously mentioned, the consequence of silver exposures via the dermal route is dermal argyria, which does not contribute to the systemic argyria induced by oral and inhalation routes of exposures. Silver has also been used in dentistry (as amalgams) and as an ingredient in mouth washes. However, there is no documented evidence of argyria developing from dental or mouth wash uses of silver despite its widespread and frequent use in dentistry for over a century; consequently, EPA concludes that the level of exposure from the dental and mouthwash uses is negligible. Therefore, EPA did not aggregate the exposures resulting from these various uses with pesticidal exposure sources.

A. Dietary Exposure

Under the current proposal (PP 7F7178), silver will be used as a sanitizer for food contact surfaces, resulting in dietary, drinking water, and residential exposures. The use sites include but are not limited to: Food service facilities, cafeterias, households, kitchens, food preparation areas, food processing equipment and treated surfaces, such as countertops, equipment, and appliances. The sanitizing solution is applied to these various surfaces by spraying (trigger, spraying, coarse pump), wiping with a cloth or sponge, mopping, or by full immersion. As a result of these uses, residues are expected to transfer to the food that comes into contact with these treated surfaces and subsequently to be ingested by humans.

1. *Food*. The Agency assessed chronic dietary exposure from the use of silver as a food contact sanitizer. The dietary assessment was only completed for chronic routes because the regulatory effect that has been identified is based on argyria, one that occurs only after chronic exposure. For dietary exposures from this product being used on countertops, the Incidental Dietary Residential Exposure Assessment Model, IDREAM™ incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-1996, and 1998 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. The maximum rate for silver is 50 ppm active ingredient.

The use on utensils, dishes and glass was assessed. Based on conservative calculations, risk concerns were identified. At this time, a label restriction will be required that prohibits the use on utensils, dishes and glassware until a residue transfer study has been conducted and accepted by the Agency.

Agricultural Premises-Dairy Facilities. Dietary exposures from these general premise uses are expected to be much lower than the dietary exposure resulting from the surface disinfectant and sanitizing uses considered for this tolerance exemption: therefore, the agricultural uses were not assessed separately. However, the sanitization of food processing equipment permits product contact with the interior of equipment. The milk-truck model (described in the FDA document, ''Sanitizing Solutions: Chemistry Guidelines for Food Additive Petitions'', pages 9-10)(FDA 2003) for these types of uses was executed in order to estimate residues that could transfer from treated surfaces to food. From this guidance, it was conservatively assumed that a child will consume 320 grams of milk per day (90th percentile value) and an adult will consume 125 grams milk per day (mean value). Because EPA has utilized this maximized value for children along with a child's body weight in this assessment, EPA has confidence that the calculations are conservative and representative of any potential risks to any population.

The Agency assumes that the sanitized tank truck which transports the milk is a conservative estimate of residue that is available in food processing facilities.

Milk undergoes no additional dilution prior to reaching the consumer and it is also assumed that 100% of the residues available post sanitation is transferred to the food.

Additionally, the dietary contribution as a result of food processing equipment sanitization is so extremely small that it is considered negligible and not included in the combined or aggregate assessments.

2. *Drinking water exposure*. There are no outdoor or potable human drinking water system uses for the use of silver proposed in pesticide petition (PP) 7F7178. In addition, the uses identified as indoor hard surface applications will result in minimal, if any, runoff of silver into the surface water. The use of silver as a food contact surface sanitizer will result in minimal, if any, runoff of silver into the surface water. This use will result in an insignificant contribution to drinking water exposures. In addition to sanitization, silver is registered as an active ingredient in water filters. The bacteriostatic water filters are impregnated with silver and may result in residues in the drinking water supply. However, the levels of available residues resulting from impregnated water filters are much less when in comparison to the amount of residues that will be available for intake when silver-containing liquid concentrates are used. As a result, any drinking water exposures from the new use of silver are assumed to be negligible. Additionally, any drinking water risks from impregnated filters are assumed to be represented by the dietary risks resulting from hard surface sanitization. The Agency believes that an assessment of any potential risks resulting from silver in drinking water is not warranted at this time.

Therefore, based on the uses of silver outlined in the pesticide petition, the Agency believes that risks resulting from silver in drinking water will be negligible and that an assessment is not warranted at this time.

Table 1 provides a comprehensive summary of all of the use patterns potentially resulting in dietary exposure that were considered for this tolerance exemption.

TABLE 1.—POTENTIAL USE SCENARIOS

Use Site Category	Example Use Sites	Scenarios
Use Site Category I: Agricultural Premises and Equipment	Dairy farms, hog farms, equine farms	Application to hard surface (feeding dishes, bottling equipment, floors, etc) through coarse spraying (low pressure spray), trigger pump spray, wipe/sponge, mop, and immersion
Use Site Categories II, III, and V: Food Handling, Commercial/Institutional/Industrial, Medical	Food processing plants; Hospitals; Public places (e.g., restaurants, hotel/motel rooms); Medical/Dental offices; Nursing home; Schools, Cruise ships, Dining Halls.	Application to hard surfaces through coarse spraying (low pressure spray), trigger pump spray, wipe/sponge, mop, and immersion. Some examples of surfaces include: sinks, cutting boards, counter tops, kitchen appliances, breast pumps and parts, baby bottles, ice chests, and various others that are summarized on the proposed label.
Use Site Category IV: Residential and Public Access Premises	Homes, kitchens	Application to hard surfaces through coarse spraying (low pressure spray), trigger pump spray, wipe/sponge, mop, and immersion. Examples of the hard surfaces include those identified for Use Site Categories II, III, and V.

B. Other Non-Occupational Exposure

The residential exposure assessment considers all potential non-occupational pesticide exposure, other than exposure due to residues in food or in drinking water. Exposures may occur during and after application on hard surfaces (e.g., floors). Each route of exposure (incidental oral, dermal, inhalation) is considered where appropriate. The risks to handlers are quantitatively assessed based on the nature of the chemical. As previously stated, there are no adverse toxicological consequences (systemic or irritation) resulting from contact with silver other than skin discoloration. Residential exposures are short-term (< 30 days) and intermediate-term (1 to 6 months) in nature. As supported in the toxicological discussion, however, silver ion produces only cosmetic effects and only as a result of chronic exposures. In addition, incidental ingestion (hand to mouth behavior of a child on a treated floor) as well as dermal exposures resulting from a child contacting a freshly cleaned floor are considered short-term in duration.

Based on the fact that silver will exist in the ionic form, which does not volatilize, any post-application inhalation exposures to vapors are expected to be negligible. Essentially, there are no toxicological consequences (systematic or irritation) resulting from contact with silver other than discoloration. Table 2 outlines the use patterns and routes of exposure that were considered for purposes of a non dietary residential assessment. The Agency will request that label claim be placed on the label to advise users that prolonged contact with the product may cause skin discoloration.

Other non-pesticidal industrial uses of silver include, but are not limited to, photography, cosmetics, sunscreens, manufacture of inks and dyes, mirror production, and in jewelry. All these uses may result in exposures via the dermal route, which over a chronic duration, may cause skin discoloration. However, dermal exposures resulting from these uses are not appropriate to include in this aggregate exposure assessment. It has been previously concluded that systemic uptake and distribution of silver does not occur via the dermal route. The specific uses of silver that were considered for this aggregate assessment include the cleansing of hard surfaces in various food handling, institutional, medical and residential premises. Exposures

resulting from freshly cleaned surfaces are considered not to be of concern to the Agency.

TABLE 2.—REPRESENTATIVE USES ASSOCIATED WITH RESIDENTIAL EXPOSURE

Representative Use	Exposure Scenario	Application Method	Application Rate
Indoor Hard Surfaces	ST Handler: Dermal and Inhalation;	Liquid Pour	4.17 E-04 lb ai/gal (0.005% ai x 8.34 lb/gal)
	ST and IT Post-app[1]: child incidental ingestion and dermal	Mopping Wiping Trigger Pump Spray Low Pressure Spray (coarse spray) Immersion[2]	50 ppm silver ion

ST = Short-term exposure, IT = Intermediate-term exposure

[1] IT post-application exposures to children were assessed because this product could be used in a commercial day care facility.

[2] The handler exposures associated with liquid pouring of this product are representative of those associated with immersion (standing solution).

V. Cumulative Effects

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider ''available information'' concerning the cumulative effects of a particular pesticide's residues and ''other substances that have a common mechanism of toxicity.''

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding between silver and any other substances and silver does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance exemption action, therefore, EPA has not assumed that silver has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism on EPA's website at *http://www.epa.gov/pesticides/cumulative*.

VI. Safety Factor for Infants and Children-

1. *In general*. Section 408(b)(2)(C) of FFDCA provides that EPA shall apply an additional tenfold (10X) margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the database on toxicity and exposure unless EPA determines based on reliable data that a different margin of safety will be safe for infants and children. This additional margin of safety is commonly referred to as the FQPA safety factor (SF). In applying this provision, EPA either retains the default value of 10X, or uses a different additional safety factor when reliable data available to EPA support the choice of a different factor.

2. *Prenatal and postnatal sensitivity*. There is extensive data and analysis on silver's toxicity in the historical data/literature and the regulatory advisories established by other Federal Agencies, which do not indicate an increased susceptibility of children to the toxic effects of silver. A NTP developmental toxicity study concluded that the NOAEL recorded for developmental toxicity in rats receiving gavage doses of silver acetate, was greater than 100 mg/kg when the test material was administered on gestation days 6 through 19. No increase in susceptibility was apparent in this study. Furthermore, silver nitrate has been used for decades to treat neonatal conjunctivitis. Finally, there is no reason to believe that the effects that are observed following the administration of silver would warrant additional safety factors for children. The skin is the target organ and the deposition of silver should not be age dependent. Moreover, because EPA believes that the Gaul and Staud study adequately characterizes variability in human sensitivity, EPA is not applying an intra-species uncertainty factor in deriving the chronic RfD for silver.

3. *Conclusion*. Although EPA is not applying an inter-species uncertainty factor (because of reliance on human data) or an intra-species uncertainty factor (because human sensitivity has been adequately characterized), EPA is retaining the 10X FQPA safety factor in assessing oral risk to address the fact that the dose used to determine the chronic RfD showed effects from silver (argyria). In making this determination, EPA took into account that argyria is not a toxic effect, there is no evidence of increased sensitivity in the young, and the exposure assessment for silver is very conservative.

For dermal exposure, silver ions tend to bind to the skin and do not penetrate the skin to cause systemic effects. Thus, systemic uptake and distribution of silver does not occur following dermal exposure. Skin discoloration is the only effect due to a localized reaction. Based on the above findings, a FQPA safety factor of 1X should be applied to the chronic dietary RfD for assessing dermal exposure. An additional safety factor is not required for the protection of infants and children because there would not be an increase in susceptibility to this cosmetic nontoxic effect. This cosmetic event is a function of the dermal contact dose not age. Furthermore, the approach taken to assess risk from dermal exposure is very conservative in that the Agency has based its dermal risk assessment on the systemic oral dose that was used to establish the oral/dietary risks.

VII. Aggregate Risks and Determination of Safety

Safety is assessed for acute and chronic risks by comparing aggregate exposure to the pesticide to the acute population adjusted dose (aPAD) and chronic population adjusted dose (cPAD). The aPAD and cPAD are calculated by dividing the LOC by all applicable uncertainty/safety factors. For linear cancer risks, EPA calculates the probability of additional cancer cases given aggregate exposure. Short-term, intermediate-term, and long-term risks are evaluated by comparing aggregate exposure to the LOC to ensure that the margin of exposure (MOE) called for by the product of all applicable uncertainty/safety factors is not exceeded.

For a tolerance to be found to be safe, it must be shown ''that there is reasonable certainty that no harm will

result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information.'' Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

1. *Dietary risk*. A summary of antimicrobial indirect food use acute/chronic risk estimates from exposure to treated countertops are shown below in Table 3. As explained above, EPA believes that exposures resulting from silver in drinking water will be negligible. For adults, chronic dietary exposure risk estimates are approximately 20% of the chronic PAD. For children, the most highly exposed population subgroup, the chronic dietary risk estimates are 62% of the chronic PAD. Therefore, chronic dietary exposure estimates are below the Agency's level of concern for all population subgroups.

TABLE 3.—CALCULATED EXPOSURE AND RISK RESULTING FROM SILVER SANITIZATION OF COUNTERTOPS

Exposure Group	Chronic	
	DDD(mg/kg/d) [a]	%cPAD [b]
Adult males (13+)	0.00022	22
Adult females (13-69)	0.00021	21
Children (1-2)	0.00062	62

[a] DDD (mg/kg/day) was provided from the IDREAM model.

[b] % PAD = exposure (total dietary exposure)/ PAD) x 100. The cPAD is equivalent to the chronic oral RfD value of 0.001mg/kg/day.

2. *Aggregate non-cancer risk*. Aggregate exposure takes into account residential exposure plus chronic exposure to food and water (considered to be a background exposure level). Because any oral residential exposures will be short-term in nature, the chronic risk is equal to the estimate for dietary risk.

3. *Aggregate cancer risk for U.S. population*. Available animal and human experience through occupational and medicinal exposure scenarios have not indicated a carcinogenic potential for silver. Therefore, silver is not expected to be carcinogenic to humans particularly in light of its low systemic toxicity potential and our understanding of its metabolism.

4. *Determination of safety*. Based on these risk assessments, EPA concludes that there is reasonable certainty that no harm will result to the general population or to infants and children from aggregate exposure to silver residues.

VIII. Other Considerations

A. Analytical Enforcement Methodology

An analytical method for food is not needed. Food contact sanitizers are typically regulated by state health departments to ensure that the food industry is using these products in compliance with the regulations in 40 CFR 180.940. The end use solution that is applied to the food contact surface is analyzed rather than food items that may come into contact with the treated surface. An analytical method is available to analyze the use dilution that is applied to food contact surfaces. The following methods of analysis are used to analyze the use dilution of silver being applied to food contact surfaces: Gas chromatography (GC), infrared (IR), ultraviolet absorption (UV), nuclear magnetic resonance (NMR).

B. International Residue Limits

There is not a Codex Maximum Residue Level established for silver.

IX. Statutory and Executive Order Reviews

This final rule establishes a tolerance under section 408(d) of FFDCA in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled *Regulatory Planning and Review* (58 FR 51735, October 4, 1993). Because this rule has been exempted from review under Executive Order 12866, this rule is not subject to Executive Order 13211, *Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001) or Executive Order 13045, entitled *Protection of Children from Environmental Health Risks and Safety Risks* (62 FR 19885, April 23, 1997). This final rule does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 *et seq.*, nor does it require any special considerations under Executive Order 12898, entitled *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under section 408(d) of FFDCA, such as the tolerance in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*) do not apply.

This final rule directly regulates growers, food processors, food handlers and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (65 FR 67249, November 6, 2000) do not apply to this rule. In addition, This rule does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act of 1995 (UMRA) (Public Law 104-4).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act of 1995 (NTTAA), Public Law 104-113, section 12(d) (15 U.S.C. 272 note).

X. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, generally provides that before a rule may take effect, the agency promulgating the rule must submit a rule report to each House of the Congress and to the Comptroller General of the United States. EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of this final rule in the **Federal Register**. This final rule is not a ''major rule'' as defined by 5 U.S.C. 804(2).

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Food contact sanitizers, Silver, Food additives, Pesticides and pests,

Reporting and recordkeeping requirements.

Dated: May 26, 2009.

Joan Harrigan-Farrelly,

Director, Antimicrobials Division, Office of Pesticide Programs.

■ Therefore, 40 CFR chapter I is amended as follows:

PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

■ 2. Section 180.940 is amended by adding alphabetically the following entry to the table in paragraph (a):

§ 180.940 Tolerance exemptions for active and inert ingredients for use in antimicrobial formulations (Food-contact surface sanitizing solutions).

* * * * *

(a) * * *

Pesticide Chemical	CAS Reg. No.	Limits
	* * * * * * *	
Silver ions resulting from the use of electrolytically-generated silver ions stabilized in citric acid as silver dihydrogen citrate (does not include metallic silver)	14701–21–4	When ready for use, the end-use concentration of silver ions is not to exceed 50 ppm of active silver.
	* * * * * * *	

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[FR Doc. E9–13476 Filed 6–9–09; 8:45 am]

BILLING CODE 6560–50–S

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 73

[DA 09–1209; MB Docket No. 08–126; RM–11458]

Television Broadcasting Services; Canton, OH

AGENCY: Federal Communications Commission.

ACTION: Final rule.

SUMMARY: The Commission grants a petition for rulemaking filed by Trinity Christian Center of Santa Ana, Inc., d/b/a Trinity Broadcasting Network (''Trinity''), the licensee of station WDLI–DT, to substitute DTV channel 49 for its assigned post-transition DTV channel 39 at Canton, Ohio.

DATES: This rule is effective June 10, 2009.

FOR FURTHER INFORMATION CONTACT: David J. Brown, Media Bureau, (202) 418–1600.

SUPPLEMENTARY INFORMATION: This is a synopsis of the Commission's *Report and Order,* MB Docket No. 08–126, adopted May 28, 2009, and released May 29, 2009. The full text of this document is available for public inspection and copying during normal business hours in the FCC's Reference Information Center at Portals II, CY–A257, 445 12th Street, SW., Washington, DC 20554. This document will also be available via ECFS (*http://www.fcc.gov/cgb/ecfs/*). (Documents will be available electronically in ASCII, Word 97, and/or Adobe Acrobat.) This document may be purchased from the Commission's duplicating contractor, Best Copy and Printing, Inc., 445 12th Street, SW., Room CY–B402, Washington, DC 20554, telephone 1–800–478–3160 or via the Internet *http://www.BCPIWEB.com.* To request this document in accessible formats (computer diskettes, large print, audio recording, and Braille), send an e-mail to *fcc504@fcc.gov* or call the Commission's Consumer and Governmental Affairs Bureau at (202) 418–0530 (voice), (202) 418–0432 (TTY). This document does not contain information collection requirements subject to the Paperwork Reduction Act of 1995, Public Law 104–13. In addition, therefore, it does not contain any information collection burden ''for small business concerns with fewer than 25 employees,'' pursuant to the Small Business Paperwork Relief Act of 2002, Public Law 107–198, *see* 44 U.S.C. 3506(c)(4). Provisions of the Regulatory Flexibility Act of 1980 do not apply to this proceeding.

The Commission will send a copy of this *Report and Order* in a report to be sent to Congress and the Government Accountability Office pursuant to the Congressional Review Act, *see* 5 U.S.C. 801(a)(1)(A).

List of Subjects in 47 CFR Part 73

Television, Television broadcasting.

■ For the reasons discussed in the preamble, the Federal Communications Commission amends 47 CFR Part 73 as follows:

PART 73—RADIO BROADCAST SERVICES

■ 1. The authority citation for part 73 continues to read as follows:

Authority: 47 U.S.C. 154, 303, 334, 336.

§ 73.622 [Amended]

■ 2. Section 73.622(i), the Post-Transition Table of DTV Allotments under Ohio, is amended by adding DTV channel 49 and removing DTV channel 39 at Canton.

Federal Communications Commission.

Clay C. Pendarvis

Associate Chief, Video Division, Media Bureau.

[FR Doc. E9–13650 Filed 6–9–09; 8:45 am]

BILLING CODE 6712–01–P

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 73

[DA 09–1225; MB Docket No. 08–129; RM–11461]

Television Broadcasting Services; Spokane, WA

AGENCY: Federal Communications Commission.

ACTION: Final rule.

SUMMARY: The Commission grants a petition for rulemaking filed KHQ, Incorporated (''KHQ''), the licensee of station KHQ–DT, DTV channel 7, Spokane, Washington, and a related petition for rulemaking filed by Spokane School District #81 (''Spokane School District''), the licensee of noncommercial educational station KSPS–DT, DTV channel *8, Spokane, Washington. KHQ requests the substitution of DTV channel 15 for its assigned post-transition DTV channel 7 at Spokane, and the Spokane School District requests the substitution of DTV channel *7, its current analog channel, for its assigned post-transition DTV channel *8 at Spokane.

DATES: This rule is effective June 10, 2009.

FDA U.S. FOOD & DRUG ADMINISTRATION

Inventory of Effective Food Contact Substance (FCS) Notifications

FCN No. 1569

Pure Bioscience, Inc.

According to Section 409(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act, food contact substance notifications (FCNs) are effective only for the listed manufacturer and its customers. Other manufacturers must submit their own FCN for the same food contact substance and intended use.

Food Contact Substance:	A solution of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid
Notifier:	Pure Bioscience, Inc.
Manufacturer/Supplier:	Pure Bioscience, Inc.
Intended Use:	As an antimicrobial solution applied by spray or dip to reduce the pathogen populations on poultry carcasses, parts and organs. (See Limitations/Specifications)
Limitations/Specifications*:	For use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses parts and organs. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.
Effective Date:	Dec 18, 2015
National Environmental Policy Act (NEPA) Submission:**	Environmental Assessment (in PDF)[6] (640 kb)
FDA Decision:	Finding of No Significant Impact (FONSI)[7]

*See Food Types and Conditions of Use for Food Contact Substances[8].

**More about Environmental Decisions[9] and Definitions of Environmental Terms[10].
See also Inventory of Environmental Impact Decisions for Food Contact Substance Notifications[11].

Links on this page:

1. http://www.addthis.com/bookmark.php?u508=true&v=152&username=fdamain
2. http://www.addthis.com/bookmark.php
3. http://www.fda.gov/default.htm
4. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/default.htm
5. http://www.fda.gov/food/ingredientspackaginglabeling/ucm112642.htm
6. http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/UCM488859.pdf
7. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm488455.htm
8. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/FoodTypesConditionsofUse/default.htm
9. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm
10. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105934.htm
11. http://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN

Page Last Updated: 11/30/2016

Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

FDA U.S. FOOD & DRUG ADMINISTRATION

Inventory of Effective Food Contact Substance (FCS) Notifications

FCN No. 1600

Pure Bioscience, Inc.

According to Section 409(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act, food contact substance notifications (FCNs) are effective only for the listed manufacturer and its customers. Other manufacturers must submit their own FCN for the same food contact substance and intended use.

Food Contact Substance:	A solution of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid.
Notifier:	Pure Bioscience, Inc.
Manufacturer/Supplier:	Pure Bioscience, Inc.
Intended Use:	As an antimicrobial solution applied by spray or dip on fruits and vegetables intended for processing (see Limitations/Specifications).
Limitations/Specifications*:	For use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to fruits and vegetables intended for processing. The FCS is not intended for use on any citrus fruit nor is it for use on grapes intended for winemaking. The FCS is not for use in combination with any other silver containing antimicrobial.
Effective Date:	Jan 7, 2016
National Environmental Policy Act (NEPA) Submission:**	Environmental Assessment (in PDF)[6] (613 kb)
FDA Decision:	Finding of No Significant Impact (FONSI)[7]

*See Food Types and Conditions of Use for Food Contact Substances[8].

**More about Environmental Decisions[9] and Definitions of Environmental Terms[10].
See also Inventory of Environmental Impact Decisions for Food Contact Substance Notifications[11].

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2. http://www.addthis.com/bookmark.php
3. http://www.fda.gov/default.htm
4. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/default.htm
5. http://www.fda.gov/food/ingredientspackaginglabeling/ucm112642.htm
6. http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/UCM490022.pdf
7. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm488563.htm
8. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/FoodTypesConditionsofUse/default.htm
9. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm
10. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105934.htm
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Page Last Updated: 11/30/2016

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5. http://www.fda.gov/food/ingredientspackaginglabeling/ucm112642.htm
6. http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/UCM490022.pdf
7. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm488563.htm
8. http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/FoodTypesConditionsofUse/default.htm
9. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm
10. http://www.fda.gov/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105934.htm
11. http://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN

NSF International / Nonfood Compounds Registration Program

April 22, 2011

Ms. Dolana Blount
PURE Bioscience
1725 Gillespie Way
El Cajon, CA 92020
United States

RE: PURE HARD SURFACE
Category Code: D2
NSF Registration No. 144518

Dear Ms. Dolana Blount:

NSF has processed the application for Registration of **PURE HARD SURFACE** to the NSF International Registration Guidelines for Proprietary Substances and Nonfood Compounds (2009), which are available at www.nsfwhitebook.org. The NSF Nonfood Compounds Registration Program is a continuation of the USDA product approval and listing program, which is based on meeting regulatory requirements including FDA 21 CFR for appropriate use, ingredient and labeling review.

This product is acceptable for use as a sanitizer on all surfaces not always requiring a rinse (D2) in and around food processing areas. Before using this compound, food products and packaging materials must be removed from the room or carefully protected. A potable water rinse is not required following the use of this compound on previously cleaned hard surfaces provided that the surfaces are adequately drained before contact with food so that little or no residue remains which can adulterate or have a deleterious effect on edible products. A potable water rinse is required following use of this compound under conditions other than those stated above. The compound must always be used according to applicable label directions.

NSF Registration of this product is current when the NSF Registration Number, Category Code, and Registration Mark appear on the NSF-approved product label, and the Registered product name is included in the current NSF White Book Listing of Nonfood Compounds at the NSF website (www.nsfwhitebook.org). The NSF Registration Mark can be downloaded by clicking the "Download Registration Mark" link on the NSF website (www.nsfwhitebook.org).

NSF Listing of all Registered Nonfood compounds by NSF International is not an endorsement of those compounds, or of any performance or efficacy claims made by the manufacturer.

Registration status may be verified at any time via the NSF website, at www.nsfwhitebook.org. Changes in formulation or label, without the prior written consent of NSF, will void Registration, and will supersede the on-line listing.

Sincerely,

Clifton Mclellan
NSF Nonfood Compounds Registration Program

Company No: C0075838

USDA

United States Department of Agriculture

Food Safety and
Inspection Service

Office of Policy and
Program Development

Risk, Innovations, &
Management Staff
Patriot Plaza III

1400 Independence
Avenue, SW,
Washington, D.C.
20250-3700

June 30, 2016

Ms. Bridget Tinsley
Bridget C. Tinsley-Cormier
Vice President, Market Development
PURE Bioscience, Inc.
1725 Gillespie Way
El Cajon, CA 92020

Dear Ms. Tinsley:

This letter is in response to your June 16, 2016, notification to list PURE Bioscience's food contact notification (FCN) 1569 antimicrobial for the applications on poultry carcasses, parts and organs in the Food Safety and Inspection Service (FSIS) Directive 7120.1 (Log Number 16-ING- 2036-N-A).

FSIS has completed its review of your request and has no objection to the use of FCN 1569 as an antimicrobial solution used at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses, parts and organs. Please contact Ms. Rosalyn Murphy-Jenkins at (301) 504-0879 or via email at rosalyn.murphy-jenkins@fsis.usda.gov, if you have questions on labeling.

The use of this antimicrobial, as described in your notification, will need to be addressed in an establishment's hazard analysis and, as appropriate, incorporated into a Hazard Analysis and Critical Control Point (HACCP) plan, Sanitation Standard Operating Procedures (SSOPs), or other prerequisite program, validated for its application, and verified on an "on-going" basis for its effectiveness. If the establishment does not address the effects of using FCN 1569 in its hazard analysis, FSIS would be unable to determine that product produced using FCN 1569 is not adulterated, and, therefore, the product would not be eligible to bear the mark of inspection. This letter should not be considered as validation that your chemical or process would be effective in any particular official establishment.

As described in the FR Notice Vol. 70, No. 201, Pages 60784-60786, dated October 19, 2005, a summary description on your new ingredient will be posted on the Food Safety and Inspection Service New Technology Information Table. If you do not object within five business days from the date that you receive this letter, the Agency will post the

included description of the technology on the Web site. If you do object to the description, you should state in writing that you object to the description, explain the basis for your objection (for example, proprietary agreement, confidential commercial information, etc.), and provide an alternate description. FSIS will post the alternate description, unless the Agency concludes that the description does not fairly describe the technology. In such a case, FSIS will post the description that it has prepared and will notify the company of its decision. The FSIS will post the following summary of your new ingredient:

Log Number	Company Name	Summary of the Notification/Protocol	Regulatory Waiver
16-ING-2036-N-A	PURE Bioscience	An antimicrobial solution that can be used at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses parts and organs.	N/A

FSIS Directive 7120.1, "Safe and Suitable Ingredients Used in the Production of Meat, Poultry, and Egg Products," will be amended to include the use of FCN 1569 in poultry products as shown below. The amendment will be included in the next scheduled revision of FSIS Directive 7120.1.

SUBSTANCE	PRODUCT	AMOUNT	REFERENCE	LABELING REQUIREMENTS
		Antimicrobials		
An aqueous solution of silver dihydrogen citrate	As an antimicrobial solution applied by spray or dip on poultry carcasses, parts and organs. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.	For use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses parts and organs.	Food Contact Substance Notification No. FCN 1569	None under the accepted conditions of use (6)

6) Food Contact Substance (FCS) subject to food contact notifications (FCN) is defined as any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.

Any future changes to this ingredient must be submitted to the Project Manager, Dr. John Hicks, with the Risk, Innovations, and Management Staff (RIMS) prior to implementation.

Any additional questions should be directed to Dr. John Hicks at (301) 504-0840 or via email at john.hicks@fsis.usda.gov.

Sincerely,

William K. Shaw, Jr., PhD
Director
Risk, Innovations and Management Staff
Office of Policy and Program Development

Enclosure

FCN 1569.pdf

Attachment 3

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 0 9 2009

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Elizabeth Anne Brown
Authorized Agent for,
ETI H2O
1725 Gillespie Way
El Cajon, CA 92020

Mail to: Steptoe and Johnson
1330 Connecticut Ave., N.W.
Washington, D.C. 20036-1796

Subject: Steptoe and Johnson
EPA Registration Number 72977-1
Your Amendment Dated April 16th, 2009
EPA Received Date April 16th, 2009

The amendment referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA, as amended, to modify the sources of the starting material, add a new alternate process, revise the basic and alternate Confidential Statements of Formula to reflect the revised suppliers and addresses, and revise and update the product labeling, is acceptable.

The requirements as per PR Notice 91-2 have been satisfied. The nominal concentration of the active ingredients, silver and citric acid, as shown in the updated basic Confidential Statement of Formula and Alternate formulation #1, agreed with the percentages declared on the product labeling. Additionally, the proposed new Alternate Formulation #2, dated 3/30/09, met all the requirements of PR Notice 91-2.

The upper and lower certified limits for both the active and inert ingredients are accepted.

The active and inert ingredients utilized in the proposed updated and new formulations are cleared for use in pesticide formulations.

The updated Group A product chemistry data is acceptable.

A stamped copy of labeling is enclosed for your records.

A copy of the efficacy reviews dated 09/13/07 is enclosed.

If you have any questions concerning this letter, please contact Karen M. Leavy at (703)-308-6237.

Sincerely,

Marshall Swindell
Product Manager 33
Regulatory Management Branch I
Antimicrobial Division(7510C)

April 15, 2009

AXENOHL®

Stabilized Ionic Silver

For Use in the Manufacture Of Antimicrobial Products For Commercial, Institutional and Home Use

Active Ingredient	
Silver*	0.24%
Citric Acid	20.66%
Other Ingredients	79.10%
	Total 100.00%

* Electrolytically generated Silver ions

KEEP OUT OF REACH OF CHILDREN

CAUTION

SEE SIDE PANEL FOR PRECAUTIONARY STATEMENTS

EPA REG. No. 72977-1
EPA EST. No. 72977-CA-001

Manufactured by ETI H_2O,
A Division of PURE Bioscience
1725 Gillespie Way
El Cajon, CA 92020

Deleted: Innovative Medical Services

[Batch number]

ACCEPTED
with COMMENTS
EPA Letter Dated:

JUL - 9 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-1

NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text is informational only and not part of the label. Batch number may be placed on the label or on the container itself.

PRECAUTIONARY STATEMENTS

HAZARDSTO HUMANS AND DOMESTIC ANIMALS
CAUTION

FIRST AID	
If in eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eyes. • Call a poison control center or doctor for treatment advice.
• HOT LINE NUMBER	
• Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact CHEMTREC 1-800-424-9300 for emergency medical treatment information.	

ENVIRONMENTAL HAZARDS

This pesticide is toxic to fish and aquatic invertebrates

This statement will be used on any refillable container.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing. Store in in original container

Pesticide Disposal: To avoid wastes, use all material in this container by application according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry).

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a national Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA.

Container Handling: Refillable Container. Refill this container with pesticide only. Do not reuse this container for any other purpose. Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller.

To clean the container before final disposal, empty the remaining contents from this container into a mix tank or storage tank. Fill the container about 1/4 full with solvent used in the end use product. Replace and tighten closures. Agitate vigorously or recirculate water with a pump for 2 minutes. Pour or pump rinsate into mix tank or rinsate collection system for later use or disposal. Repeat this rinsing procedure two more times

ACCEPTED
with COMMENTS
EPA Letter Dated:
JUL - 9 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 7969-1

NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text is informational only and not part of the label. Batch number may be placed on the label or on the container itself.

This statement will be used on any nonrefillable container

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing. Store in in original container

Pesticide Disposal: To avoid wastes, use all material in this container by application according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry).

Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a national Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA.

Container Handling: Nonrefillable Container. Do not reuse or refill this container. Triple rinse container (or equivalent) promptly after emptying. Offer for recycling if available.

Directions for Use

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

For Manufacturing Use Only:

For formulation of antimicrobial end use products for the following uses:

Cleaning products, specialty industrial products, products for commercial, institutional and industrial premises and equipment, or products for use in indoor residential premises.

Formulators using this product are responsible for obtaining registrations for their own end use products. This product may be used to formulate products for specific uses not listed on this label if the formulator has complied with US EPA data requirements regarding the support of such uses.

US Patents [insert applicable US patent number(s)]
Other patents pending
Made in the USA [may include US Flag symbol]

ACCEPTED
with COMMENTS
EPA Letter Dated:

JUL - 9 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-1

NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text is informational only and not part of the label. Batch number may be placed on the label or on the container itself.

Formatted Table

Deleted: STORAGE AND DISPOSAL¶ **Storage** ... [1]

Deleted: This product is intended for use in manufacturing disinfectant products. Formulators are responsible for obtaining registrations for their own end use products.¶

Deleted: For Manufacturing Use Only: Dilute 1 part of Axenohl product with 199 parts of 4.76% citric acid in water.

STORAGE AND DISPOSAL

Storage	Do not contaminate water, food or feed by storage or disposal.
Disposal	**Pesticide Disposal:** Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a national Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA. **Container Disposal:** Triple rinse. Then offer for recycling or reconditioning, or puncture and dispose of in a sanitary landfill, or by other procedures approved by state and local authorities

ACCEPTED
with COMMENTS
EPA Letter Dated:

JUL - 9 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-1

ESL 08/21/2009 Amendment 2/11/2010

Axen® 30

[Disinfectant], [Fungicide] [& Virucide*]

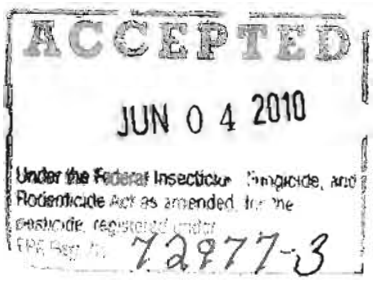
[Disinfects and Deodorizes]
[Restaurants] • [Hospitals] • [Schools] • [Homes] • [Offices] • [Trucks] • [Trailers] • [Shipping Containers]
• [Rail Cars]

Manufactured by ETI H2O
A Division of PURE Bioscience
1725 Gillespie Way
El Cajon, CA 92020
EPA REG. No. 72977-3
EPA EST. No. 72977-CA-001
Net Vol.
[Batch Number – may appear on container]

Active Ingredient	
Silver†	0.003%
Citric Acid	4.846%
Other Ingredients	95.151%
Total	100.000%

† Electrolytically generated Silver ions

KEEP OUT OF REACH OF CHILDREN



NOTE: [Bracketed] text is optional wording ***Bold/italicized test is information only and not part of the label.***

DIRECTIONS FOR USE

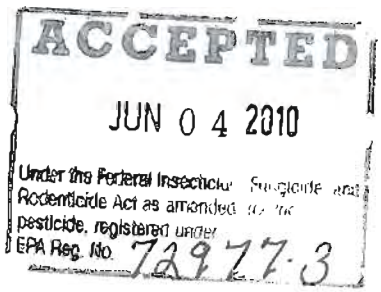
It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

AXEN® 30 [this product] is a colorless, odorless broad spectrum antimicrobial disinfectant and deodorizer. Proven to kill bacteria, fungus and viruses*, **AXEN® 30** [this product] should be used on non-porous environmental hard surfaces in ***Choose from the list below***

Homes [households]
offices
hospitals
nursing homes
medical clinics
dental clinics
infirmary
blood bank(s)
pharmacies
laboratories
funeral homes
veterinary clinics
animal shelters
kennels
cages
stables
catteries
animal transport vehicles
ambulances
patient transfer vehicles
hotels
restaurants
bars
supermarket[grocery store]
schools
colleges
dorm rooms [dormitories]
churches
shelters
military [installations] [locations]
day care facilities
daycare centers
nurseries
playrooms
playgrounds
recreational facilities
prisons [jails]
kitchens
[public] restrooms
bathrooms
washrooms
laundry rooms
bedrooms
basements
garage(s)
workshops
attics
locker rooms
exercise facilities
gyms [gymnasium]
beauty shops or salons)
barber shops
spas
health clubs
laundromats
airports
school buses
cars [autos]
RV [mobile home]
trucks
trailers
shipping containers
rail cars
subways
trains
airplanes
ships
cruise ships
busses
other public transportation vehicles

AXEN® 30 [this product] has been formulated to disinfect hard, non-porous environmental surfaces (painted, glazed tile, plastic, metal, glass, glazed porcelain) and objects including ***Choose from the list below***

walls
floors
counters
cabinets [cabinet handles]
sinks
tubs
exterior toilet [urinal] surfaces
faucet handles
showers
doorknobs
handrails
light switch covers
telephones
remote control (s)
appliances
stove tops
bed frames
wheelchairs
over-bed tables
examination tables
waste containers
tables
chairs
patio furniture
equipment tables
lab benches
[AC] [heating] vents
children's toys
toys
toy boxes
play tables
jungle gyms
playhouses
baby furniture
child car seats, hard surfaces only
booster chairs [seats]
strollers [stroller handles]
cribs
playpens
activity centers
diaper pails
diaper changing tables
potty[training] seats
laundry hampers
bathroom counters
kitchen counters
desks
grocery carts
computer keyboards
tanning beds
sports equipment
pharmacy equipment
FLAVORx® equipment
Pharmacy dispensing equipment
cat litter boxes
animal cages [carriers]



NOTE: [Bracketed] text is optional wording ***Bold/Italicized test is information only and not part of the label.***

ESL 08/21/2009

Amendment 2/11/2010

General Information

AXEN® 30 [this product] **successfully killed the following organisms under AOAC protocols (In order to ensure that all organisms listed are killed, you must use the contact times as directed in the Application Instructions):**

Organism	Kill Time
‡*Pseudomonas aeruginosa*	30 seconds
‡*Salmonella enterica*	30 seconds
Staphylococcus aureus	2 minutes
Listeria monocytogenes	2 minutes
Vancomycin resistant *Enterococcus faecium (VRE)*	2 minutes
Methicillin resistant *Staphylococcus aureus (MRSA)*	2 minutes
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA)*	2 minutes
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA-PVL)*	2 minutes
Escherichia coli O157:H7	2 minutes
Acinetobacter baumannii	2 minutes
Campylobacter jejuni	2 minutes
Trichophyton mentagrophytes (Athlete's Foot Fungus)	10 minutes
‡*HIV type 1- [Strain HTLV IIIB]	30 seconds
*Herpes Simplex Type 1 [VR-733 F(1) Strain]	1 minute [60 seconds]
*Rotavirus	3 minutes
*Human Coronavirus	3 minutes
*Influenza A (H1N1)	1 minute [60 seconds]
*Swine Influenza A (H1N1)	1 minute [60 seconds]
*Respiratory Syncytial Virus [RSV]	3 minutes
*Adenovirus Type 2	3 minutes
*Equine Herpes Virus Type 1	3 minutes
*Murine Norovirus	10 minutes
* Norovirus [as Feline Calicivirus]	10 minutes
*Avian Influenza A	10 minutes
*Influenza A [VR-544, Hong Kong strain]	10 minutes
*Rhinovirus [R37 VR-1147, Strain 151-1]	10 minutes
*Polio Type 2, [VR-1002, Lansing Strain]	10 minutes

[Fungicidal Activity: AXEN® 30 [this product] is effective against *Trichophyton mentagrophytes*, the Athlete's foot fungus, Use in locker rooms, dressing rooms, shower and bath areas, and exercise facilities.]

[Deodorizes: AXEN® 30 [this product] reduces annoying odors caused by bacteria. Use to control odors in hospitals, nursing homes, public restrooms, animal kennels and barn stalls. In private homes, use in the kitchen, bathroom, sink rooms and basements.]

APPLICATION INSTRUCTIONS

Pre-clean surfaces prior to using this product.

General Disinfection:
For general disinfection and control of the bacteria *Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella enterica, Listeria monocytogenes*, Vancomycin Resistant *Enterococcus faecium* (VRE), Methicillin Resistant *Staphylococcus aureus* (MRSA), Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA)*, Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA-PVL), Escherichia coli* O157:H7, *Acinetobacter baumannii and Campylobacter jejuni* the surface must be completely wet with **AXEN® 30** [this product] for 2 minutes. The surface may then be wiped dry with a clean towel. When used as directed, **AXEN® 30™** [this product]provides residual protection from *Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella enterica* up to 24 hours after initial application. Do not [touch] [contact] treated surface after application if residual protection is to be maintained..

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill bacteria, [apply] [spray] [mist] **Axen30** [this product] to the surface until thoroughly wet for 2 minutes. The surface may then be wiped dry with a clean towel. When used as directed, **AXEN® 30** [this product] provides residual protection from *Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella enterica* up to 24 hours after initial application. Do not [touch] [contact] treated surface after application if residual protection is to be maintained.

NOTE: {Bracketed} text is optional wording ***Bold/italicized test is information only and not part of the label.***

Fungus Control:
For effective control of the fungus *Trichophyton mentagrophytes*, the surface must be completely wet with **AXEN® 30** [this product] for 10 minutes. The surface may then be wiped dry with a clean towel. Re-apply when cleaning or when new growth appears.

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill fungus, [apply] [spray] [mist] **AXEN® 30** [this product] to the surface until thoroughly wet for 10 minutes. The surface may then be wiped dry with a clean towel. Re-apply when cleaning or when new growth appears.

***Viral Control:**
To kill Herpes Simplex Type 1 [F(1) Strain], Rotavirus, Human Coronavirus, Norovirus [as Feline Calicivirus], Murine Norovirus [MNV-1), Influenza A (H1N1), Swine Influenza A (H1N1), Avian Influenza A, Influenza A Virus [Hong Kong strain], Rhinovirus [R37 Strain 151-1], Respiratory Syncytial Virus [RSV], Adenovirus Type 2, Equine Herpes Virus Type 1 and Polio Virus Type 2 [Lansing Strain] the surface must be completely wet with **AXEN® 30** [this product] for 10 minutes. The surface may then be wiped dry with a clean towel.

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill viruses, [apply] [spray] [mist] **AXEN® 30** [this product] to the surface until thoroughly wet for 10 minutes. The surface may then be wiped dry with a clean towel.

Note to Reviewer: The following are optional phrases as outlined in the EPA's Guidance for Testing and Labeling Claims against Pandemic 2009 H1N1 Influenza A Virus (Formerly called Swine Flu)

[Respiratory illnesses attributable to Pandemic 2009 H1N1are caused by influenza A virus. **AXEN® 30** [This product] is a broad-spectrum hard surface disinfectant that has been shown to be effective against [Influenza A Virus (H1N1)], [Influenza A Virus (H3N2)], [Avian Influenza A Virus] and [Swine Influenza A Virus (H1N1)] and is expected to inactivate all Influenza A viruses including Pandemic 2009 H1N1 (formerly called swine flu).]

AXEN® 30 [[This product] has demonstrated effectiveness against Influenza A virus and is expected to inactivate all influenza A viruses including Pandemic 2009 H1N1 influenza A virus.]

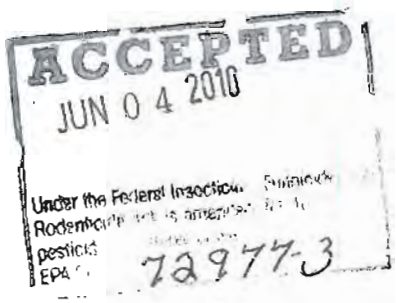
Kills HIV-1 on pre-cleaned environmental surfaces/objects previously soiled with blood/body fluids in health care settings (or other settings in which there is an expected likelihood of soiling of inanimate surfaces/objects with blood or body fluids, and in which the surfaces/objects likely to be soiled with blood or body fluids can be associated with the potential for transmission of HIV): **Instructions for Cleaning and Decontamination Against HIV** on pre-cleaned environmental surfaces/objects previously soiled with blood/body fluids: **Personal Protection**: When handling items soiled with blood or body fluids, use appropriate barrier protection such as latex gloves, gowns, masks and eye coverings. **Cleaning Procedure:** Blood and other body fluids must be thoroughly cleaned from surfaces and objects before application of this disinfectant. **Contact Time**: Apply **AXEN® 30** [this product] to area to be treated. The surface must be completely wet with **AXEN® 30** [this product] for 30 seconds. The surface may then be wiped dry with a clean towel. This contact time will not control all organisms listed on this label. Refer to application instructions for other organisms. **Disposal of Infectious Materials:** Blood and other body fluids should be autoclaved and disposed of according to federal, state and local regulations for infectious waste disposal.

KEY: The following language will be printed on the label of products intended to be sold to health facilities:

This product is not to be used as a terminal sterilant/high level disinfectant on any surface or instrument that (1) is introduced directly into the human body, either into or in contact with the human body, either into or in contact with the bloodstream, or normally sterile areas of the body, or (2) contacts intact mucous membranes but which does not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body. This product may be used to pre-clean or decontaminate critical or semi-critical medical devices prior to sterilization or high level disinfection.

Optional refill instructions
To refill [spray bottles]:

1. [REMOVE] Remove trigger sprayer [or cap] from empty bottle
2. [POUR] Remove cap from refill and pour contents directly into empty [bottle].
3. [USE] Replace trigger sprayer and use as you normally would.



NOTE: [Bracketed] text is optional wording ***Bold/Italicized test is information only and not part of the label.***

This statement will be used on NONREFILLABEL CONTAINERS.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing.
Pesticide Disposal: Nonrefillable Container. Do not reuse or refill this container –or- [Refill only with this product. Do not reuse or refill except as described in the directions for use.]. If empty: Place in trash or offer for recycling if available. Rinse thoroughly before discarding in trash or recycling.

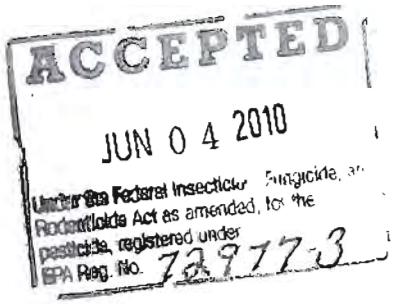
This statement will be used on REFILLABLE CONTAINERS (typically 55 gallons or larger).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing. Store in original container
Pesticide Disposal: To avoid wastes, use all material in this container by application according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry).
Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a national Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA.
Container Handling: Refillable Container. Refill this container with pesticide only. Do not reuse this container for any other purpose. Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller.
To clean the container before final disposal, empty the remaining contents from this container into a mix tank or storage tank. Fill the container about 1/4 full with solvent used in the end use product. Replace and tighten closures. Agitate vigorously or recirculate water with a pump for 2 minutes. Pour or pump rinsate into mix tank or rinsate collection system for later use or disposal. Repeat this rinsing procedure two more times

IN CASE OF EMERGENCY

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact CHEMTREC 1-800-424-9300 *(or other emergency service provider)* for emergency medical treatment information.

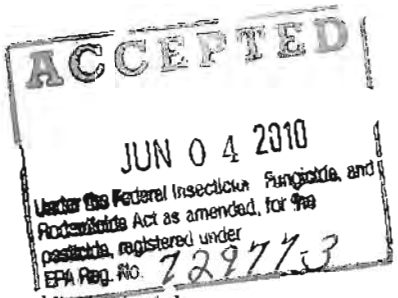


NOTE: [Bracketed] text is optional wording ***Bold/italicized test is Information only and not part of the label.***

Optional Marketing Phrases

[Kills] [Eliminates] [Effective against] *Choose one or more from the list below:*

Salmonella enterica [in 30 seconds‡]
Pseudomonas aeruginosa [in 30 seconds‡]
Staphylococcus aureus
Listeria monocytogenes
Acinetobacter baumannii [in 2 minutes]
Campylobacter jejuni [in 2 minutes]
MRSA *or* [Methicillin Resistant Staph] *or [*Methicillin Resistant *Staphylococcus aureus]*
CA-MRSA *or* [Community Associated MRSA] *or* [Community Associated Methicillin Resistant *Staphylococcus aureus*]
CA-MRSA-PVL
VRE *or* [Vanocomycin-resistant Enterococcus] *or* [Vancomycin resistant Enterococcus faecium]
Escherichia coli O157:H7
Tricophyton mentagrophytes
HIV [in 30 seconds‡]
Herpes Simplex Virus
Influenza A Virus
Rhinovirus
Polio Virus Type 1
Rotavirus
Human Coronavirus
Norovirus virus (as Feline Calicivirus)
Avian influenza A on pre-cleaned environmental hard surfaces
Respiratory Syncytial Virus (RSV)
Adenovirus [type 2]
Influenza A (H1N1) [in 1 minute]
Swine Influenza A (H1N1) [on pre-cleaned environmental hard surfaces] [in 1 minute]
Equine Herpes virus type 1
Murine Norovirus [in the presence of 5% soil]



Kills germs in 30 seconds‡
Kills common household germs
Kills germs [on surfaces you touch most]
Kills common household germs including [*Salmonella enterica], [Staphylococcus aureus], [Listeria monocytogenes]*, and [*E. coli].*
Kills [*Salmonella], [Staphylococcus], [Listeria]*, and [*E. coli].*
Kills – [Bacteria], [Fungus] and [Virus*]
Disinfects common household surfaces
Kills [common] cold] and [flu] virus[s]
Can help reduce the risk [danger] of cross contamination
Disinfectant, Fungicidal & Virucidal Spray
[Patented] Silver [Ion] Formula
No dulling residue
Disinfects without bleaching
No harsh chemical smell
Odorless
Disinfects household surfaces
No Mixing Required
Powered by [Axenohl®] [SDC 2400] [Axenohl Alternate brand name]
For daily use
Refill
[Worldwide] Patented formula
[U.S.Patent(s) 6,197,814 ; 6,583,176, [additional patent numbers as issued]
Other patents pending
Use for a [fresh] [home] [environment] [kitchen]
Commercial [Line] [Disinfectant]
Industrial [Line] [Disinfectant]
Hospital [Line] [Disinfectant]
Healthcare [Line] [Disinfectant]
Consumer [Line] [Disinfectant]
Retail [Line] [Disinfectant]
Freight [Line] [Disinfectant]
Janitorial [Line] [Disinfectant]

Optional marketing phrases continued

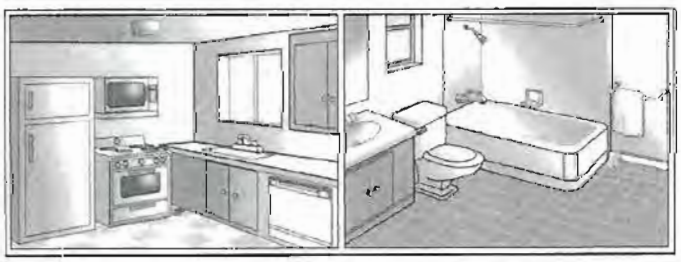
Janitorial Disinfectant

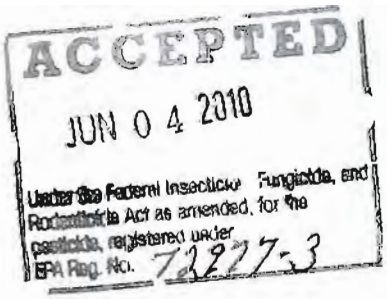
NOTE: [Bracketed] text is optional wording *Bold/italicized test is Information only and not part of the label.*

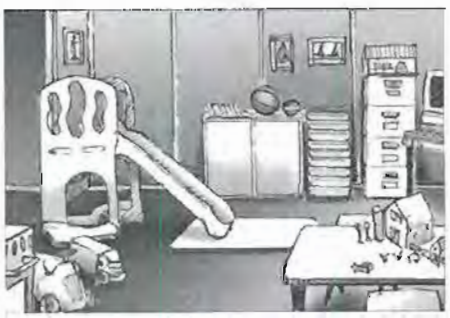
Odoban® [Commercial], [Janitorial], [Earth Choice] (use restricted to the trademark owner)
[FAST], [EASY], [EFFECTIVE]
[Antimicrobial] [antibacterial] disinfectant
Leaves surfaces disinfected
For use on high touch surfaces
Travel size
For use in *(insert use site from label)*
For use on *(insert use surface from label)*
[Ideal for] [Formulated for] [Hospitality Environment(s)] [Institutional] [Childcare Environment(s)] [Medical Environment(s)] [Nursing Environment(s)] [Healthcare Environment(s)] [Athletic Environment(s)] [Educational Environment(s)]
A New Generation of Protection
A New Generation Disinfectant
As seen on TV *may include graphic*

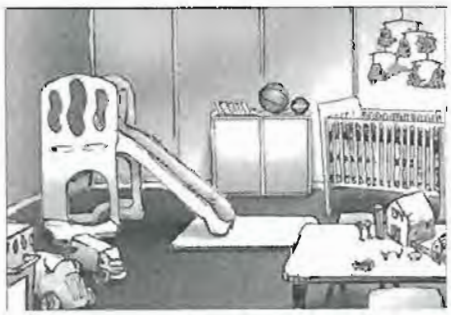
Made in the USA [may include graphic of American flag]
This product has demonstrated effectiveness against Influenza A Virus [Avian Influenza A Virus] [Swine Influenza A Virus) and is expected to inactivate all Influenza A viruses including Pandemic 2009 H1N1 (formerly called swine flu).
Kills Pandemic 2009 H1N1 influenza A virus (formerly called swine flu).
Kills Pandemic 2009 H1N1 influenza A virus.
Use to disinfect FLAVORx® equipment
Recommended for use on FLAVORx® equipment

KEY:
***-Refer to viruses ‡-Refer to organisms controlled with 30 second kill time**
Optional graphics for back of label (graphics are larger here than they will appear on the label)









NOTE: [Bracketed] text is optional wording ***Bold/italicized test is information only and not part of the label.***

U.S. ENVIRONMENTAL PROTECTION AGENCY
Office of Pesticide Programs
Antimicrobials Division (7510C)
1200 Pennsylvania Avenue NW
Washington, D.C. 20460

NOTICE OF PESTICIDE:
x Registration
__ Reregistration

(under FIFRA, as amended)

EPA Reg. Number:	Date of Issuance:
72977-4	AUG 0 6 2009

Term of Issuance:

Name of Pesticide Product: Axen 50

Name and Address of Registrant (include ZIP Code):

ETI H2O, Inc.
1725 Gillespie Way
El Cajon, CA 92020

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number.

On the basis of information furnished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA sec 3(c)(7)(B) provided that you:

1. Submit and/or cite all data required for registration of your product under FIFRA sec. 3(c)(5) when the Agency requires all registrants of similar products to submit such data; and submit acceptable responses required for re-registration of your product under FIFRA section 4.

2. Make the labeling changes listed below before you release the product for shipment:

a. Add the phrase "EPA Registration Number 72977-4."

Signature of Approving Official:

Marshall Swindell
Product Manager-33
Regulatory Management Branch I
Antimicrobials Division (7510P)

Date: AUG 0 6 2009

EPA Form 8570-6

The revised Confidential Statement of Formula dated January 8, 2007, is acceptable.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA sec. 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Sincerely,

Marshall Swindell
Product Manager 33
Regulatory Branch I
Antimicrobials Division (7510P)

Enclosure: (Stamped Labeling)

Axen50

[Sanitizer for Food Contact Surfaces]
[Food Contact Surface Sanitizer]

Active Ingredients

Silver*	0.005%
Citric Acid	5.000%
Other Ingredients	94.995%
Total	100.000%

*electrolytically generated silver ions stabilized in citric acid as silver dihydrogen citrate

KEEP OUT OF REACH OF CHILDREN
[This statement may appear on the front or back of the label]

EPA Reg. No. 72977-
EPA Est. No. (insert establishment number here)
Net Contents: (insert container net contents here)

Manufactured by: ETI H2O, a division of PURE Bioscience
1725 Gillespie Way, El Cajon, CA 92020

ACCEPTED
with COMMENTS
EPA Letter Dated:

AUG - 6 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

Note to reviewer: The following is considered optional marketing language. Language in [ ] is considered optional or interchangeable.

[INSERT OPTIONAL MARKETING LANGUAGE ON THIS PAGE]

Colorless
Odorless
Ready-to-Use [Formula]
No mixing required
No Rinsing required
No Rinse Formula
No Rinse sanitizer
Sanitize without rinsing
Contains no [dyes] or [artificial fragrances]
For daily [use] [sanitization]
Eliminated odors caused by bacteria
Sanitizes kitchen surfaces
Household sanitizer
Institutional sanitizer

Patented formula
Commercial line
Institutional line
Consumer line

Kills 99.999% of bacteria* [in 60 seconds]
Kills 99.999% of Escherichia coli (E. coli) [in 60 seconds]
Kills 99.999% of Staphylococcus aureus (Staph) [in 60 seconds]

Powered by [Axenohl]
(Note to reviewer: Axenohl is the MUP used to make this product. We may insert any registered brand name for the MUP in this phrase)

- [This product] is an effective sanitizer for use on food contact surfaces in 60 seconds [1 minute].
- For use in [food service], [hospitality],
- For use in [households], [kitchens], [food preparation areas]
- For use in [institutional kitchens], [medical institution kitchen and dining areas], [lodging establishment kitchens and dining areas]
- For sanitizing food processing equipment, dairy and milk processing equipment, sink tops, countertops, refrigerated storage and display equipment and other hard non-porous surfaces.

For use in :

- [Restaurants], [bars], [cafeterias], [institutional kitchens], [fast food operations], [fast food restaurants], [food preparations areas], [food storage areas], [food establishments],
- [coffee shops], [donut shops], [bagel stores], [pizza parlors], [liquor stores], [delis]
- [kitchens], , [Food processing plants], [USDA inspected food-processing facilities], [dairy facilities],, [egg processing plants], [meat/poultry processing plants], [meat/poultry producing establishments], [rendering plants]

- Processing facilities for: [Food], [fish], [milk], [citrus], [fruit], [vegetables], [wine], [ice cream], [potatoes] and [beverage plants]
- [Cruise ships food contact areas], [buffet counters], [dining halls], [casinos food contact areas],

This product may be used on hard non-porous surfaces such as:

- [Plastic and other non-porous cutting boards], [plastic and other non-porous chopping blocks], [coolers], [ice chests], [refrigerator bins used for meat, vegetables, fruit and eggs], [countertops], [stovetops], [appliances], [ice machines], [highchairs], [picnic tables], [drinking fountains]
- Kitchen equipment such as: [food processors], [blenders], [trash compactors], [meat cutting machines], [meat slicing machines], [bread slicing machines], [Mixing equipment], [[Ice machines], [bottled water machines]
- [Citrus processing equipment and holding tanks]

ACCEPTED
with COMMENTS
EPA Letter Dated:

AUG - 6 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

Note to reviewer: The following is considered optional marketing language. Language in [ ] is considered optional or interchangeable.

AREAS OF USE

Use [this product] to sanitize hard nonporous food contact surfaces in:

Households
Homes
Restaurants
Eating establishments
Food processing [establishments] [plants] [facilities]
Beverage plants
Dairies
Kitchen(s)
Dining Room(s)
Lunchroom(s)
Cafeteria(s)
Bars
Institutional Kitchens
Fast food operations
Coffee shops
Donut shops
Bagel stores
Liquor stores
Deli(s) [Delicatessens]
Supermarkets
Grocery stores
Convenience stores
Snack Bars
Egg Processing Plants
Food storage areas
Food Prep [Preparation] areas [surfaces]
Salad Prep [Preparation] areas [surfaces]

TYPES OF SURFACES

Use [this product] on hard, non-porous surfaces (ie stainless steel, painted, glazed tile, plastic, glass, glazed porcelain) of

Sinks
Drain [cutting] boards
Beverage Bars
Dairy Cases
Dish racks
Dishwasher
Drainboards
Food cases
Food Contact surfaces
Food trays
High chairs
High Chair trays
Counter tops [counters]
Baby bottles
Breast Pumps
Breast Pump Parts
Kitchen appliances
Kitchen sinks
Kitchen surfaces
Lunch boxes [pails]
Pacifiers
Pet Bowls [dishes] [feeding dishes]
Salad bars
Snack counters
Stovetops
Floors
Refrigerated storage equipment
Refrigerated display equipment
Blenders
Bottling equipment
Premixing equipment
Chopping blocks
Food processors
Ice Chests
Ice machines

ACCEPTED
with COMMENTS
EPA Letter Dated:

AUG - 6 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

DIRECTIONS FOR USE

It is a violation of Federal law to use this product in a manner inconsistent with its labeling.
Do not use this product on utensils, dishes or glassware.
Prolonged contact with this product may cause skin discoloration.

NOTE TO REVIEWER: Products labeled for residential use will include the following directions for use:

[To] Sanitize Food Contact Surfaces
Pre clean item [surface] prior to sanitizing.
Spray, pour or spread [this product] on surface until thoroughly wet. Let stand for 60 seconds [one minute] and wipe with a clean towel or allow to air dry. No rinsing is required.
*[This product] kills 99.999% of Escherichia coli [E. coli] and Staphylococcus aureus [Staph].

NOTE TO REVIEWER: Products labeled for commercial/industrial use will include the following directions for use:

To sanitize food contact surfaces
or
To sanitize food processing equipment and other hard surfaces in food processing locations, dairies, restaurants and bars:

[Recommended] for sanitizing food processing equipment, dairy equipment, sink tops, countertops, refrigerated storage and display equipment, and other hard nonporous surfaces. Recommended for use in restaurants, dairies, food processing plants [establishments] [facilities] and bars.

[Clean, Rinse Sanitize]
Prior to application, remove gross food particles and soil by pre-flush or pre-scrape and when necessary, pre-soak. Thoroughly wash objects to be sanitized with a good detergent or cleaner followed by a potable water rinse prior to applying sanitizer. NO POTABLE WATER RINSE IS ALLOWED AFTER APPLICATION AS A SANITIZER.

Apply [this product] by spraying or by total immersion. Surfaces must remain wet for 60 seconds [1 minute].

If the [article] surface] can not be washed and rinsed, clean thoroughly in an appropriate fashion prior to sanitizing.

*[This product] is a ready to use sanitizer that eliminates 99.999% of the following bacteria in 60 seconds:
Escherichia coli (ATCC 11229) Staphylococcus aureus

-OR-

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG - 6 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

Prior to use in a federally inspected meat and poultry plants and dairies, food products and packaging materials must be removed from the room or carefully protected. A potable water rinse is not permitted following the use of this product as a sanitizer on previously cleaned hard, non-porous surfaces, provided that the surfaces are adequately drained before contact with food so that little or no residue remains.

Apply product to pre-cleaned hard surfaces thoroughly wetting surfaces with a cloth, mop, sponge, sprayer or by immersion. For spray applications, spray product 6 to 8 inches from surface using a trigger sprayer or coarse pump. Surfaces should remain wet for 1 minute followed by adequate draining and air drying.

*[This product] is a ready to use sanitizer that eliminates 99.999% of the following bacteria in 60 seconds:
Escherichia coli (ATCC 11229) Staphylococcus aureus

DIRECTIONS FOR SANITZING FOOD PROCESSING EQUIPMENT AND FOOD CONTACT ARTICLES REGULATED BY 21CFR Sec. 178.1010: b(22), c(17)

1. Scrape flush or presoak articles to remove gross food particles and soil.
2. Thoroughly wash articles in an appropriate detergent or cleaner.
3. Rinse articles thoroughly with potable water.
4. Sanitize articles by immersion in [this product] for 60 seconds. Articles too large for immersion should be thoroughly wetted with {this product] by rinsing, spraying or swabbing.
5. Remove immersed items from solution to drain and air dry. Non-immersed items should also be allowed to air dry.

U.S. PUBLIC HEALTH SERVICE FOOD SERVICE SANITIZATION RECOMMENDATIONS CLEANING AND SANITIZING:
Equipment and articles shall be thoroughly pre-flushed or pre-scraped and pre-soaked when necessary to remove gross food particles and soil.

1. Thoroughly wash equipment and articles in a hot detergent solution. Rinse equipment thoroughly with potable water.
2. Sanitize equipment by immersion for 60 seconds at a temperature of 75°.
3. For equipment and articles that are too large to immerse, apply [this product] by rinsing, spraying or swabbing until thoroughly wetted.
4. Allow sanitized surfaces to drain and air dry. No potable water rinse is allowed.

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG - 6 2009

Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

WISCONSIN STATE DIVISION OF HEALTH
DIRECTIONS FOR EATING ESTABLISHMENTS

1. Scrape and pre-wash articles whenever possible.
2. Wash with a good detergent or compatible cleaner.
3. Rinse with potable water
4. Sanitize in [this product] without diluting. Immerse all articles for at least one minute or for contact time specified by governing sanitary code.
5. Place sanitized articles on a rack or drain board to air dry.

NOTE: A clean potable water rinse following sanitization is not permitted under Section HFS 196.13 of the Wisconsin Administrative Code.

IN CASE OF EMERGENCY

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact CHEMTREC 1-800-424-9300 for emergency medical treatment information.

STORAGE AND DISPOSAL

Storage: Do not contaminate water, food or feed by storage or disposal.
Disposal: Do not reuse container. Rinse thoroughly before discarding in trash or recycling.

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG - 6 2009
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-4

SDC3A

[Disinfectant], [Fungicide] [& Virucide*][& Food Contact Surface Sanitizer]

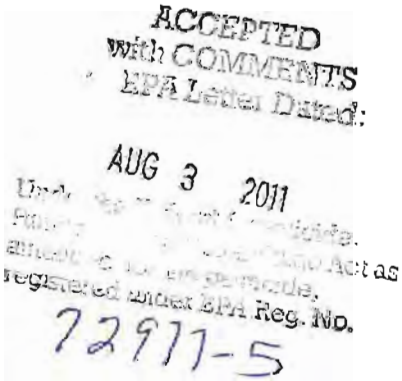
[Disinfects and Deodorizes] • [Food Contact Surface Sanitizer] • [Sanitizer for Food Contact Surfaces] • [Restaurants] • [Hospitals] • [Schools] • [Homes] • [Offices] • [Trucks] • [Trailers] • [Shipping Containers] • [Rail Cars] • [Sanitizer for food [and beverage] processing equipment [facilities]]

Active Ingredient	
Silver[1]	0.003%
Citric Acid	4.846%
Other Ingredients	95.151%
Total	100.000%

[1] Electrolytically generated silver ions stabilized in citric acid as silver dihydrogen citrate

KEEP OUT OF REACH OF CHILDREN

Manufactured by ETI H2O
A Division of PURE Bioscience
1725 Gillespie Way
El Cajon, CA 92020
EPA REG. No. 72977- 5
EPA EST. No. 72977-CA-001
Net Vol.
[Batch Number – may appear on container]



DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

[SDC3A] [this product] is a colorless, odorless, broad spectrum antimicrobial [sanitizer], disinfectant and deodorizer. Proven to kill bacteria, fungus and viruses*, **[SDC3A]** [this product] should be used on non-porous environmental hard surfaces in ***Choose from the lists below***

Note:Non food contact sites

Homes [households]
offices
hospitals
nursing homes
medical clinics
dental clinics
infirmary
blood bank[s]
pharmacies
laboratories
funeral homes
veterinary clinics
animal shelters
kennels
cages
stables
catteries
animal transport vehicles
ambulances
patient transfer vehicles
hotels
restaurants
bars
supermarket[grocery store]
schools
colleges
dorm rooms [dormitories]
churches
shelters
military [installations] [locations]
day care facilities
daycare centers
nurseries
playrooms
playgrounds
recreational facilities
prisons [jails]
kitchens
[public] restrooms
bathrooms
washrooms
laundry rooms
bedrooms
basements
garage(s)
workshops
attics
locker rooms
exercise facilities
gyms [gymnasium]
beauty shops [salons]
barber shops
spas
health clubs
laundromats
airports
school buses
cars [autos]
RV [mobile home]
trucks
trailers
shipping containers
rail cars
subways
trains
airplanes
ships
cruise ships
busses
other public transportation vehicles

Note:Food Contact sites

beverage plants
food processing plants [facilities]
food storage areas
food [beverage] prep areas
institutional kitchens
cafeterias
bars
fast food operations
coffee [donut] [bagel]shops
delis
liquor [convenience] stores
eating establishments
supermarkets [grocery stores]
snack bars
dinning rooms
lunchrooms
break rooms
dairy farms [facilities]
egg processing plants
meat [poultry] [fish]processing plants
meat [poultry] [fish]producing establishments
rendering plants
[milk] [fruit] [vegetable] [wine] [ice cream] [potato] processing facilities
[Food service] [hospitality]
Cruise ship food processing [preparation] areas
Dining halls
smokehouses

[SDC3A] [this product] has been formulated to treat hard, non-porous environmental surfaces ([painted], [glazed tile], [plastic], [non-porous vinyl], [naugahyde], [polyurethane], [plasticized PVC], [butyl rubber (EPDM)], [neoprene], [Viton®], [Teflon®], [silicone] [metal], [glass], [glazed porcelain], [acrylic], [fiberglass], [sealed granite], [sealed marble], [Formica®], [linoleum]) and objects including ***Choose from the lists below***

NOTE: Non-food contact surfaces

walls
floors
counters
cabinets [cabinet handles]
sinks
tubs
exterior toilet [urinal] surfaces
faucet handles
showers
doorknobs
handrails
light switch covers
telephones
remote controls
appliances
stove tops
bed frames
wheelchairs
over-bed tables
examination tables
waste containers
tables
chairs
patio furniture
equipment tables
lab benches
[AC] [heating] vents
children's toys
toys
pacifiers
toy boxes
play tables
jungle gyms
playhouses
baby furniture
child car seats, hard surfaces only
booster chairs [seats]
strollers [stroller handles]
cribs
playpens
activity centers
diaper pails
diaper changing tables
potty[training] seats
laundry hampers
bathroom counters
kitchen counters
grocery carts
desks
computer keyboards
tanning beds
cat litter boxes
animal cages [carriers]
pet bowls [dishes]
animal feeding dishes
non-porous athletic mats

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG 3 2011
[Product] [Pesticide]
as the pesticide,
registered under EPA Reg. No.
72977-5

NOTE: Food Contact Surfaces

counters [countertops]
dish racks
drainboards
highchairs [trays]
breast pump [parts]
lunch boxes[pails]
picnic tables
drinking fountains
kitchen surfaces
food processing equipment
bottling equipment
pre-mixing equipment
blenders
[food] processors
beverage bars [equipment]
buffet counters
salad bars
snack counters
cutting boards
plastic and other non-porous chopping blocks
coolers
ice] machines] chests
ice cream machines
[equipment]
yogurt machines
[equipment]refrigerator bins used for meat, vegetables, fruit and eggs
[refrigerated] food display equipment
food cases
dairy cases
food contact surfaces
food trays
stovetops
blenders
meat cutting machines
bread slicing machines
mixing equipment [mixers]
kitchen appliances
[meat], [fish], [poultry] washers
blanchers
dicers
slicers
grinders
shredders
stuffers
scalders
pickers
shackles
saws
trolleys
hooks
tables
hoists
sorters
scales
cones
deboners
separators
carts
racks
chiller tanks
conveyor systems
labeling machines
packaging equipment
canning equipment
descalers
skinning equipment
filleting machines
homogenizers
evaporators
dryers
clarifiers
storage tanks
cheese making equipment
processing vessels
pumps
pasteurizers
filling line equipment
Tanks
Kettles
filling, seaming, sealing and capping equipment
pulpers
juicers
millers
grinders
ovens
extractors
blanchers
refrigerators
freezers
microwaves
toasters
cooking equipment
ovens
ranges
grills
fryers
choppers
crispers
cutters
shelving
bins
cabinets
sinks
basins
faucets
bakery equipment
coffee and tea equipment
steam tables
warming equipment
concession equipment
[processing] vacuums
[processing] hand [power] tools

ACCEPTED
with COMMENTS
EPA Letter Dated:

AUG 3 2011

Under the Federal Insecticide, Fungicide and Rodenticide Act as amended for the pesticide, registered under EPA Reg. No.
72977-5

General Information

[SDC3A] [this product] successfully killed the following organisms under AOAC protocols (In order to ensure that all organisms listed are killed, you must use the contact times as directed in the Application Instructions):

Organism	Kill Time
‡*Pseudomonas aeruginosa*	30 seconds
‡ *Salmonella enterica*	30 seconds
‡ *Staphylococcus aureus*	2 minutes
‡*Listeria monocytogenes*	2 minutes
Vancomycin resistant *Enterococcus faecium (VRE)*	2 minutes
Methicillin resistant *Staphylococcus aureus (MRSA)*	2 minutes
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA)*	2 minutes
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA-PVL)*	2 minutes
Escherichia coli O157:H7	2 minutes
Acinetobacter baumannii	2 minutes
Campylobacter jejuni	2 minutes
Carbapenem resistant *Escherichia coli*	2 minutes
Carbapenem resistant *Klebsiella pneumoniae*	2 minutes
Carbapenem resistant *Klebsiella pneumonia*, NDM-1 +	2 minutes
Trichophyton mentagrophytes (Athlete's Foot Fungus)	5 minutes
[‡]*HIV type 1[Strain HTLV IIIB]	30 seconds
[‡]*Rotavirus	30 seconds
[‡]*Human Coronavirus	30 seconds
[‡]*Influenza A (H1N1)	30 seconds
[‡]*Swine Influenza A (H1N1)	30 seconds
[‡]*Respiratory Syncytial Virus [RSV]	30 seconds
[‡]*Adenovirus Type 2	30 seconds
[‡]*Avian Influenza A	30 seconds
[‡]*Influenza A [VR-544, Hong Kong strain]	30 seconds
Hepatitis B Virus (HBV) [as Duck Hepatitis B Virus]	1 minute [60 seconds]
Hepatitis C Virus (HCV) [as Bovine Diarrhea Virus]	1 minute [60 seconds]
*Murine Norovirus [MNV-1]	1 minute [60 seconds]
* Norovirus [as Feline Calicivirus]	1 minute [60 seconds]
*Herpes Simplex Type 1 [VR-733 F(1) Strain]	1 minute [60 seconds]
*Rhinovirus [R37 VR-1147, Strain 151-1]	1 minute [60 seconds]
*Polio Type 2 [VR-1002, Lansing Strain]	1 minute [60 seconds]

[Fungicidal Activity: [SDC3A] [this product] is effective against *Trichophyton mentagrophytes*, the Athlete's foot fungus, Use in locker rooms, dressing rooms, shower and bath areas, and exercise facilities.]

[Deodorizes: When used as directed, **[SDC3A]** [this product] reduces annoying odors caused by bacteria. Use to control odors in hospitals, nursing homes, public restrooms, animal kennels and barn stalls. In private homes, use in the kitchen, bathroom, sink rooms and basements.]

[**SANITIZATION: SDC3A** is a food contact surface sanitizer proven to kill 99.999% of the following bacteria in 60 seconds:
Escherichia coli *Staphylococcus aureus*
See application instructions for proper use.]

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG 3
Under the Federal Insecticide, Fungicide and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72977-5

APPLICATION INSTRUCTIONS

Pre-clean surfaces prior to using this product. [You may use this product for pre-cleaning.]

[General Cleaning: Apply to surface until thoroughly wet then wipe the surface clean.]

General Disinfection:
For general disinfection and control of the bacteria *Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella enterica, Listeria monocytogenes,* Vancomycin Resistant *Enterococcus faecium* (VRE), Methicillin Resistant *Staphylococcus aureus* (MRSA), Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA),* Community Associated Methicillin resistant *Staphylococcus aureus*

(CA-MRSA-PVL), Escherichia coli O157:H7, *Acinetobacter baumannii, Campylobacter jejuni,* Carbapenem resistant *Escherichia coli,* Carbapenem resistant *Klebsiella pneumonia,* and Carbapenem resistant *Klebsiella pneumoniae* (NDM-1 [positive] [+]) the surface must be completely wet with **[SDC3A] [this product]** for 2 minutes. The surface may then be wiped dry with a clean towel. When used as directed, [SDC3A] [this product] provides residual protection from *Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella enterica* up to 24 hours after initial application. Do not [touch] [contact] treated surface after application if residual protection is to be maintained.

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill bacteria, [apply] [spray] [mist] [SDC 3A] [this product] to the surface until thoroughly wet for 2 minutes. The surface may then be wiped dry with a clean towel. When used as directed, [SDC3A] [this product] provides residual protection from *Pseudomonas aeruginosa, Staphylococcus aureus* and *Salmonella enterica* up to 24 hours after initial application. Do not [touch] [contact] treated surface after application if residual protection is to be maintained.

Fungus Control:
For effective control of the fungus *Trichophyton mentagrophytes*, the surface must be completely wet with [SDC3A] [this product] for 5 minutes. The surface may then be wiped dry with a clean towel. Re-apply when cleaning or when new growth appears.

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill fungus, [apply] [spray] [mist] [SDC3A] [this product] to the surface until thoroughly wet for 5 minutes. The surface may then be wiped dry with a clean towel. Re-apply when cleaning or when new growth appears.

***Viral Control:**
To kill Herpes Simplex Type 1 [F(1) Strain], Rotavirus, Human Coronavirus, Influenza A (H1N1), Swine Influenza A (H1N1), Adenovirus Type 2, Respiratory Syncytial Virus [RSV], Murine Norovirus [MNV-1], Norovirus [as Feline Calicivirus], Avian Influenza A, Influenza A Virus [Hong Kong strain], Rhinovirus [R37 Strain 151-1] and Polio Virus Type 2 [Lansing Strain] the surface must be completely wet with [SDC3A] [this product] for 1 minute. The surface may then be wiped dry with a clean towel

NOTE: The following condensed instructions may be use in place of the above paragraph.
To kill viruses, [apply] [spray] [mist] [SDC3A] [this product] to the surface until thoroughly wet for 1 minute. The surface may then be wiped dry with a clean towel.

Note to Reviewer: The following are optional phrases as outlined in the EPA's Guidance for Testing and Labeling Claims against Pandemic 2009 H1N1 Influenza A Virus (Formerly called Swine Flu)

[Respiratory illnesses attributable to Pandemic 2009 H1N1are caused by influenza A virus. [SDC3A] [This product] is a broad-spectrum hard surface disinfectant that has been shown to be effective against [Influenza A Virus (H1N1)), [Influenza A Virus], [Avian Influenza A Virus] and [Swine Influenza A Virus (H1N1)] and is expected to inactivate all Influenza A viruses including Pandemic 2009 H1N1 (formerly called swine flu).]

[SDC3A] [[This product] has demonstrated effectiveness against Influenza A virus and is expected to inactivate all influenza A viruses including Pandemic 2009 H1N1 influenza A virus.]

Kills HIV-1, HBV and HCV on pre-cleaned environmental surfaces/objects previously soiled with blood/body fluids in health care settings (or *other settings in* which there is an expected likelihood of soiling of inanimate surfaces/objects with blood or body fluids, and in which the surfaces/objects likely to be soiled with blood or body fluids can be associated with the potential for transmission of HIV, HBV or HCV): **Instructions for Cleaning and Decontamination Against HIV, HBV and HCV** on pre-cleaned environmental surfaces/objects previously soiled with blood/body fluids: **Personal Protection**: When handling items soiled with blood or body fluids, use appropriate barrier protection such as latex gloves, gowns, masks and eye coverings. **Cleaning Procedure:** Blood and other body fluids must be thoroughly cleaned from surfaces and objects before application of this disinfectant. **Contact Time**: Apply **[SDC3A]** [this product] to area to be treated. Allow the surface to remain wet for 30 seconds to kill HIV-1. Use 1 minute for HBV and HCV. The surface may then be wiped dry with a clean towel. These contact times will not control all organisms listed on this label. Refer to application instructions for other organisms. **Disposal of Infectious Materials:** Blood and other body fluids should be absorbed and disposed of according to federal, state and local regulations for infectious waste disposal.

ACCEPTED
with COMMENTS
EPA Letter Date:
AUG 3 2011
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended for the pesticide registered under EPA Reg. No. 72477-5

Sanitization [of food contact surfaces]
Do not use this product on utensils, dishes or glassware.

NOTE TO REVIEWER: Products labeled only for consumer/residential/ commercial use will include the following directions for use:

[To] Sanitize Food Contact Surfaces
Spray, pour or spread [SDC3A] [this product] on surface until thoroughly wet. Let stand for 60 seconds [one minute] and wipe with a clean towel or allow to air dry. No rinsing is required.

** [SDC3A] [This product] kills 99.999% of *Escherichia coli* [E. coli] and *Staphylococcus aureus*.

NOTE TO REVIEWER: Products labeled for commercial/industrial/food processing area use will include the following directions for use:

To sanitize food contact surfaces
or
To sanitize food processing equipment and other hard surfaces in food processing locations, dairies, restaurants and bars:

[Recommended] for sanitizing food processing equipment, dairy equipment, sink tops, countertops, refrigerated storage and display equipment, and other hard nonporous surfaces. Recommended for use in restaurants, dairies, food processing plants [establishments] [facilities] and bars.

[Clean, Rinse Sanitize]
Prior to application, remove gross food particles and soil by pre-flush or pre-scrape and when necessary, pre-soak. Thoroughly wash objects to be sanitized with a good detergent or cleaner followed by a potable water rinse prior to applying sanitizer. No potable water rinse is allowed after application as a sanitizer.

ACCEPTED
With COMMENTS
EPA Letter Dated:
AUG 3 2011
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide registered under EPA Reg. No. 72977-5

Apply [SDC3A] [this product] by spraying or by total immersion. Surfaces must remain wet for 60 seconds [1 minute].

If the [article] surface] cannot be washed and rinsed, clean thoroughly in an appropriate fashion prior to sanitizing.

**[SDC3A] [This product] is a ready to use sanitizer that eliminates 99.999% of the following bacteria in 60 seconds:
Escherichia coli *Staphylococcus aureus*

-OR-

Prior to use in a federally inspected meat and poultry plants and dairies, food products and packaging materials must be removed from the room or carefully protected. A potable water rinse is not permitted following the use of this product as a sanitizer on previously cleaned hard, non-porous surfaces, provided that the surfaces are adequately drained before contact with food so that little or no residue remains.

Apply [SDC3A] [product] to pre-cleaned hard surfaces by thoroughly wetting surfaces with a cloth, mop, sponge, sprayer or by immersion. Surfaces should remain wet for 1 minute followed by adequate draining and air drying.

**[SDC3A] [This product] is a ready to use sanitizer that eliminates 99.999% of the following bacteria in 60 seconds:
Escherichia coli (ATCC 11229) Staphylococcus aureus

[DIRECTIONS FOR SANITZING FOOD PROCESSING EQUIPMENT AND FOOD CONTACT ARTICLES REGULATED BY 21CFR Sec. 178.1010: b(22), c(17)
1. Scrape flush or presoak articles to remove gross food particles and soil.
2. Thoroughly wash articles in an appropriate detergent or cleaner.
3. Rinse articles thoroughly with potable water.
4. Sanitize articles by immersion in [SDC3A] [this product] for 60 seconds. Articles too large for immersion should be thoroughly wetted with [SDC3A] [this product] by rinsing, spraying or swabbing.
5. Remove immersed items from solution to drain and air dry. Non-immersed items should also be allowed to air dry.]
[U.S. PUBLIC HEALTH SERVICE FOOD SERVICE SANITIZATION RECOMMENDATIONS CLEANING AND SANITIZING:
Equipment shall be thoroughly pre-flushed or pre-scraped and pre-soaked when necessary to remove gross food particles and soil.
1. Thoroughly wash equipment in a hot detergent solution. Rinse equipment thoroughly with potable water.
2. Sanitize equipment by immersion for 60 seconds at a temperature of 75°.
3. For equipment that is too large to immerse, apply [SDC3A] [this product] by rinsing, spraying or swabbing until thoroughly wetted.
4. Allow sanitized surfaces to drain and air dry. No potable water rinse is allowed.]

[BEVERAGE DISPENSING EQUIPMENT SANITIZER DIRECTIONS
For sanitizing of bottling or pre-mixed dispensing equipment after cleaning thoroughly rinse equipment with a potable water rinse. Fill equipment with [SDC3A] [this product] and allow to remain in the equipment for at least 60 seconds. Sanitizing solution should be drained from the system. To insure the removal of flavors, it is suggested that during changeover between products the system should be cleaned, rinsed and flushed with the sanitizing solution for at least 1 minute. Drain thoroughly and allow to air dry before reuse. No potable water rinse is allowed.]

[FOR SANITIZING IN FISHERIES, MILK, WINE, CITRUS, POTATO & ICE CREAM PROCESSING PLANTS: For use as a sanitizer on conveyor belts and equipment [to reduce or eliminate odors in the processing area]. Also for use on filling equipment to reduce bacteria. Follow directions for sanitizing food contact surfaces.]

[WISCONSIN STATE DIVISION OF HEALTH DIRECTIONS FOR EATING ESTABLISHMENTS

1. Scrape and pre-wash articles whenever possible.
2. Wash with a good detergent or compatible cleaner.
3. Rinse with potable water
4. Sanitize in [SDC3A] [this product] without diluting. Immerse all articles for at least one minute or for contact time specified by governing sanitary code.
5. Place sanitized articles on a rack or drain board to air dry.

NOTE: A clean potable water rinse following sanitization is not permitted under Section HFS 196.13 of the Wisconsin Administrative Code.]

NOTE: Optional refill instructions

To refill [spray bottles]:

1. [REMOVE] Remove trigger sprayer [or cap] from empty bottle
2. [POUR] Remove cap from refill and pour contents directly into empty [bottle].
3. [USE] Replace trigger sprayer and use as you normally would.

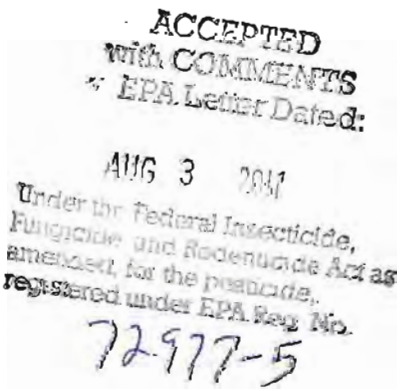
NOTE: The following language will be printed on the label of products intended to be sold to health facilities:

This product is not to be used as a terminal sterilant/high level disinfectant on any surface or instrument that (1) is introduced directly into the human body, either into or in contact with the bloodstream, or normally sterile areas of the body, or (2) contacts intact mucous membranes but which does not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body. This product may be used to pre-clean or decontaminate critical or semi-critical medical devices prior to sterilization or high level disinfection.

NOTE: The following may only be used on the back or side panel of the label if a supplemental registrant obtains an NSF listing:

-OR-

[NSF Listed]
[Include NSF Listing Number]



This statement will be used on NONREFILLABEL CONTAINERS.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing.
Pesticide Disposal: Nonrefillable Container. Do not reuse or refill this container –or- [Refill only with this product. Do not reuse or refill except as described in the directions for use.]. If empty: Place in trash or offer for recycling if available. Rinse thoroughly before discarding in trash or recycling.

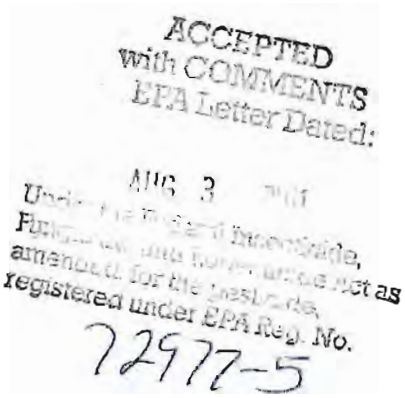
This statement will be used on REFILLABLE CONTAINERS (typically 55 gallons or larger).

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing. Store in original container.
Pesticide Disposal: To avoid wastes, use all material in this container by application according to label directions. If wastes cannot be avoided, offer remaining product to a waste disposal facility or pesticide disposal program (often such programs are run by state or local governments or by industry).
Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a national Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA.
Container Handling: Refillable Container. Refill this container with pesticide only. Do not reuse this container for any other purpose. Cleaning the container before final disposal is the responsibility of the person disposing of the container. Cleaning before refilling is the responsibility of the refiller.
To clean the container before final disposal, empty the remaining contents from this container into a mix tank or storage tank. Fill the container about 1/4 full with solvent used in the end use product. Replace and tighten closures. Agitate vigorously or recirculate water with a pump for 2 minutes. Pour or pump rinsate into mix tank or rinsate collection system for later use or disposal. Repeat this rinsing procedure two more times

IN CASE OF EMERGENCY

Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact [CHEMTREC 1-800-424-9300] or [the National Pesticide Information Center at 1-800-858-7378, Monday through Friday, 9 a.m. to 5 p.m] for emergency medical treatment information.



Optional marketing phrases

[Kills] [Eliminates] [Effective against] [Defends against] *Choose one or more from the list below:*

- *Salmonella enterica* [in 30 seconds†]
- *Pseudomonas aeruginosa* [in 30 seconds†]
- *Staphylococcus aureus*
- *Listeria monocytogenes*
- *Acinetobacter baumannii* [in 2 minutes]
- *Campylobacter jejuni* [in 2 minutes]
- MRSA *or* [Methicillin Resistant Staph] *or* [Methicillin Resistant *Staphylococcus aureus*]
- CA-MRSA *or* [Community Associated MRSA] *or* [Community Associated Methicillin Resistant *Staphylococcus aureus*]
- CA-MRSA-PVL
- VRE *or* [Vancomycin-resistant Enterococcus] *or* [Vancomycin resistant Enterococcus faecium]
- Escherichia coli O157:H7 [E. coli]
- Carbapenem resistant *Escherichia coli* [in 2 minutes]
- Carbapenem resistant *Klebsiella pneumoniae* [in 2 minutes]
- Carbapenem resistant *Klebsiella pneumoniae [(NDM-1 [+] [positive])]* [in 2 minutes]
- Tricophyton mentagrophytes
- HIV [in 30 seconds†]
- Herpes Simplex Virus [in 1 minute]
- Influenza A Virus [in 30 seconds†]
- Rhinovirus [in 1 minute]
- Polio Virus Type 1 [in 1 minute]
- Rotavirus [in 30 seconds†]
- Human Coronavirus [in 30 seconds†]
- Norovirus [as Feline Calicivirus] [in 1 minute]
- Avian Influenza A on pre-cleaned environmental hard surfaces [in 30 seconds†]
- Respiratory Syncytial Virus [RSV] [in 30 seconds†]
- Adenovirus [type 2] [in 30 seconds†]
- Influenza A (H1N1) [in 30 seconds†]
- Swine Influenza A (H1N1) [in 30 seconds†]
- Murine Norovirus [in 1 minute]
- Hepatitis B Virus [HBV] [in 1 minute]
- Hepatitis C Virus [HCV] [in 1 minute]

Kills germs in 30 seconds†
Kills common household germs
Kills germs [on surfaces you touch most]
Kills common household germs including [*Salmonella enteric*], [*Staphylococcus aureus*], [*Listeria monocytogenes*], and [*E. coli*].
Kills [*Salmonella*], [*Staphylococcus*], [*Listeria*], and [*E. coli*].
Kills - Bacteria, Fungus and Virus*
Disinfects [Defends against] common household surfaces
Kills [Defends against] [common] [cold] and [flu] virus[s]
Defends against germs that can make you sick
Disinfectant, Fungicidal & Virucidal* Spray
Can help reduce the risk [danger] of cross contamination
[Effective against] [Kills] multiple drug resistant bacterium
Fast acting disinfectant
Designed for practical use
Designed to save you time
Inspired by how you want [need] to disinfect
Invented to disinfect the way you want [need]
Your time is important so our kill times are fast
Meets EPA requirements for Toxicity Category IV
[Patented] Silver [Ion] Formula
No dulling residue
[Compatible with] [Safe for use on] [most] hard non-porous surfaces
Disinfects without bleaching
No harsh chemical smell
Odorless
Fragrance free
Contains no [dyes] or [artificial fragrances]
Contains [no] [non] VOC emitting ingredients
Ammonia free [formula]

Bleach free [formula]
Alcohol free [formula]
Phenol free [formula]
Contains no phosphates
Does not contain [chlorine] bleach [or] [ammonia] [alcohol] [phenols]
[This product] contains no [chlorine] bleach [alcohol] [phosphates] [or ammonia]
Colorless
Ready-to-Use [Formula]
No mixing required
Eliminates odors caused by bacteria
Disinfects household surfaces
No Mixing Required
Powered by [Axenohl®] [SDC 2400] [Axenohl Alternate brand name]
For daily use
Refill
[Worldwide] Patented formula
[U.S. Patent(s) 6,197,814 ; 6,583,176, 7,261,905, [additional patent numbers as issued]
Other patents pending
Use for a [fresh] [home] [environment] (kitchen]
Commercial [Line] [Disinfectant]
Industrial [Line] [Disinfectant]
Hospital [Line] [Disinfectant]
Consumer [Line] [Disinfectant]
Retail [Line] [Disinfectant]
Freight [Line] [Disinfectant]
Janitorial [Line]
Janitorial Disinfectant
Cruise Line Disinfectant
[FAST], [EASY], [EFFECTIVE]
[Antimicrobial] [antibacterial] disinfectant
Leaves surfaces disinfected
For use on high touch surfaces
Travel size
For use in *(insert use site from label)*
For use on *(insert use surface from label)*
[Ideal for] [Formulated for] [Hospitality Environment(s)] [Institutional] [Childcare Environment(s)] [Medical Environment(s)] [Nursing Environment(s)] [Healthcare Environment(s)] [Athletic Environment(s)] [Educational Environment(s)]
A New Generation of Protection
A New Generation Disinfectant
As seen on TV *may include graphic*

Made in the USA [may include graphic of American flag]
[SDC3A] [This product] has demonstrated effectiveness against Influenza A Virus [Avian Influenza A Virus] [Swine Influenza A Virus] and is expected to inactivate all Influenza A viruses including Pandemic 2009 H1N1 (formerly called swine flu).
Kills Pandemic 2009 H1N1 influenza A virus (formerly called swine flu).
Kills Pandemic 2009 H1N1 influenza A virus.

The following phrases can also be used for products labeled as a food contact sanitizer
No Rinsing required
No Rinse Formula
No Rinse sanitizer
Sanitize without rinsing
For daily [use] [sanitization]
Sanitizes kitchen surfaces
Household sanitizer
Institutional sanitizer
Kills 99.999% of bacteria [in 60 seconds]**
Kills 99.999% of Escherichia coli (E. coli) [in 60 seconds]**
Kills 99.999% of Staphylococcus aureus [in 60 seconds]**
Kills 99.999% of bacteria that cause food borne illnesses (food poisoning]
Effective sanitizer for food contact surfaces

For use in [insert one or more of the use sites listed on the label]
For use on [insert one or more of the use surfaces listed on the label]
For sanitizing [insert one or more of the food contact use surfaces]
No [measuring] [mixing] required
Effective sanitizer for food [and beverage] processing equipment [facilities]

KEY: *-Refer to viruses ‡-Refer to organisms controlled with 30 second kill time
**** Refers to sanitizer claims**

ACCEPTED
With COMMENTS
EPA Letter Dated:
AUG 3 2011
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended for the pesticide, registered under EPA Reg. No. 72977-5

These or similar optional graphics may be used to demonstrate use sites (graphics are larger here than they will appear on the label)



THE FOLLOWING TABLE IS OPTIONAL TEXT:

[

Organism	ID
Pseudomonas aeruginosa	ATCC#15442
Staphylococcus aureus '	ATCC#6538
Salmonella enterica '	ATCC#10708
Listeria monocytogenes '	ATCC#19111
Vancomycin resistant *Enterococcus faecium (VRE)*	ATCC#700221
Methicillin resistant *Staphylococcus aureus (MRSA)*	ATCC#700698
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA)*	NRS123, USA 400
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA-PVL)*	NRS 192
Escherichia coli O157:H7	ATCC#43888
Acinetobacter baumannii	ATCC#19606
Campylobacter jejuni	ATCC#29428
Carbapenem resistant *Escherichia coli*	BSLI#082710-EcCP1
Carbapenem resistant *Klebsiella pneumoniae*	BSLI#081710KPC4
Carbapenem resistant *Klebsiella pneumoniae* , NDM-1 +	ATCC#BAA-2146
Trichophyton mentagrophytes (Athlete's Foot Fungus)	ATCC#9533
*HIV type 1- Strain HTLV IIIB	HTLV-IIIB
*Herpes Simplex Type 1 VR-733 F(1) Strain	ATCC VR-733
*Rotavirus	Strain WA, Ottawa
*Human Coronavirus	ATCC VR-740
*Influenza A (H1N1)	ATCC VR-1469
*Swine Influenza A (H1N1)	ATCC VR-333
*Respiratory Syncytial Virus [RSV]	ATCC VR-26
*Adenovirus Type 2	ATCC VR-846
*Murine Norovirus	MNV-1.CW1
*Norovirus [as Feline Calicivirus]	ATCC VR-782
*Avian Influenza A	ATCC VR-2072
*Influenza A [VR-544, Hong Kong strain]	ATCC VR-544
*Rhinovirus [R37 VR-1147, Strain 151-1]	ATCC VR-1147
*Polio Type 2, [VR-1002, Lansing Strain]	ATCC VR-1002
Hepatitis B Virus (HBV) [as Duck Hepatitis B Virus]	Hepadnavirus Testing, Inc., Lot 7/31/07 pool
Hepatitis C Virus (HCV) [as Bovine Diarrhea Virus]	Strain Oregon C24v-genotype 1

]

ACCEPTED
with COMMENTS
EPA Letter Dated:
AUG 3 2011
Under the Federal Insecticide, Fungicide, and Rodenticide Act as amended, for the pesticide, registered under EPA Reg. No. 72-777-5

OCT 9 2009

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA United States Environmental Protection Agency **Office of Pesticide Programs**

ETI H2O
1725 Gillespie Way
El Cajon, CA 92020

AGENT: Steptoe and Johnson
1330 Connecticut Avenue, N.W.
Washington, D. C. 20036-1795

Attention: Elizabeth Anne Brown, Ph.D.

Subject: SDC0240CP
EPA Registration No. 76977-6
Amendment Dated October 7, 2009

The amendment, submitted in connection with registration under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), as amended, is acceptable.

- To address label wording modifications in the Directions for use

A stamped copy of the "accepted" product labeling is enclosed for your records.

If you have any questions regarding this letter, please contact Demson Fuller at (703) 308-8062.

Sincerely,

Marshall Swindell
Product Manager 33
Regulatory Management Branch 1
Antimicrobials Division (7510P)

Enclosure

SDC0240CP

Bacteriostatic Humidifier Water Treatment

[Controls build up of bacteria and algae in water tanks of [portable] [and/or] [console] humidifier[s] [units]]

Active Ingredients	
Silver*	0.24%
Citric Acid	20.66%
Other Ingredients	79.10%
Total	100.00%

* Electrolytically generated Silver ions

KEEP OUT OF REACH OF CHILDREN

CAUTION

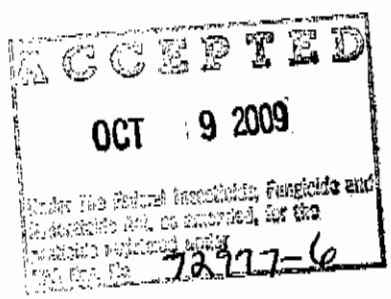
See [side panel] [inside label] for additional precautionary statements]

EPA REG. No. 72977-6
EPA EST. No. XXXXX-XX-XXX

Manufactured by ETI H_2O,
A Division of PURE Bioscience
1725 Gillespie Way
El Cajon, CA 92020

[Batch number – may appear on bottle]

Net Contents:



NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text in informational only and not part of the label. Batch number may be placed on the label or on the container itself.

DIRECTIONS FOR USE
It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

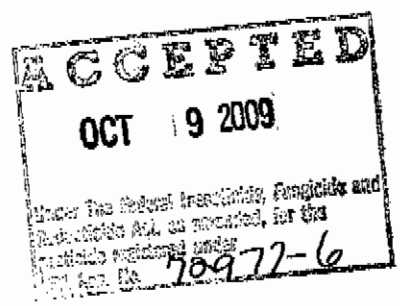
This product is for the control of bacteria and algae in humidifier water tanks. Thoroughly clean humidifier water tank and filters before each heating season. SDC0240CP is designed for use in portable [and/or console] humidifiers. SDC0240CP is not for use in heat vaporizing or atomizing type vaporizer humidifiers.

Note to reviewer: The following directions will be used for containers that do not include a dosing device/dropper.
For every 3 gallons of water contained in the humidifier tank, add one teaspoon (5 ml) of [SDC0240CP] [this product]. Repeat this process when refilling tank.

This product will stain fabrics if contacted.

Note to reviewer: The following directions will be used for containers that include a dosing device/dropper.
For every half gallon of water added to the humidifier tank, add one dropper filled to the double line (0.75 ml or 0.025 fl. oz.) with [SDC0240CP] [this product]. Do not use the dropper for any other purpose.

This product will stain fabrics if contacted.



NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text in informational only and not part of the label. Batch number may be placed on the label or on the container itself.

PRECAUTIONARY STATEMENTS
HAZARDS TO HUMANS AND DOMESTIC ANIMALS

CAUTION. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, using tobacco or using the toilet.

FIRST AID	
If in eyes	• Hold eye open and rinse slowly and gently with water for 15-20 minutes. • Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eyes. • Call a poison control center or doctor for treatment advice.
• HOT LINE NUMBER	
• Have the product container or label with you when calling a poison control center or doctor, or going for treatment. You may also contact CHEMTREC 1-800-424-9300 for emergency medical treatment information.	

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.
Pesticide Storage: Store in a cool, dry area away from direct sunlight at temperatures above freezing. Store in original container in areas inaccessible to individuals unfamiliar with use.
Pesticide Disposal and Container Handling: Nonrefillable Container. Do not reuse or refill this container. Wrap container and put in trash or offer for recycling if available. If partly filled: Call your local solid waste agency for disposal instructions. Never place unused product down any indoor or outdoor drain.

Optional phrases for labeling or label packaging.

Ready to use
Odorless
Colorless
Non-corrosive to humidifier parts
Controls buildup of bacteria and algae in portable [and/or console] humidifier water tanks
Control odors caused by bacteria and algae in portable [and/or console] humidifier water tanks
For use in manually filled humidifier water tanks
Easy to use
Powered by [SDC Ag+] [Silver science] [SDC]
Patented Formula
US Patents [insert applicable patent number(s)]
Helps control bacteria in water tanks
Helps control algae build-up in water tanks
[Helps] Eliminate[s] unpleasant odors
[For] use in evaporative [cool mist] humidifiers
Made in the USA [include us flag symbol]
Results may vary according to water quality
Dosing Dropper included *Note: Based upon container*
[One bottle] treats XX gallons *Note: Based upon container size*

ACCEPTED
OCT 9 2009
Under The Federal Insecticide, Fungicide and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No. 72977-6

NOTE TO REVIEWER: [Bracketed text] is optional wording. Bold and italicized text in informational only and not part of the label. Batch number may be placed on the label or on the container itself.

ESL 08/21/2009 Amendment 2/11/2010

THE FOLLOWING TABLE IS OPTIONAL TEXT:

[

Organism	ID
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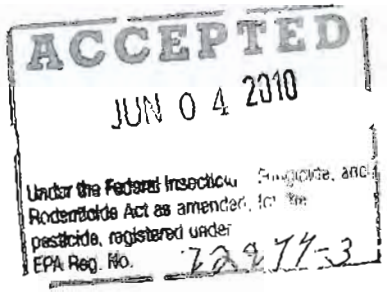
Staphylococcus aureus	ATCC#6538
Salmonella enterica	ATCC#10708
Listeria monocytogenes	ATCC#19111
Vancomycin resistant *Enterococcus faecium (VRE)*	ATCC#700221
Methicillin resistant *Staphylococcus aureus (MRSA)*	ATCC#700698
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA)*	NRS123, USA 400
Community Associated Methicillin resistant *Staphylococcus aureus (CA-MRSA-PVL)*	NRS 192
Escherichia coli O157:H7	ATCC#43888
Acinetobacter baumannii	ATCC#19606
Campylobacter jejuni	ATCC#29428
Trichophyton mentagrophytes (Athlete's Foot Fungus)	ATCC#9533
**HIV* type 1- Strain HTLV IIIB	HTLV-IIIB
*Herpes Simplex Type 1 VR-733 F(1) Strain	ATCC VR-733
*Rotavirus	Strain WA, Ottawa
*Human Coronavirus	ATCC VR-740
*Influenza A (H1N1)	ATCC VR-1469
*Swine Influenza A (H1N1)	ATCC VR-333
*Respiratory Syncytial Virus [RSV]	ATCC VR-26
*Adenovirus Type 2	ATCC VR-846
*Murine Norovirus	MNV-1.CW1
* Norovirus [as Feline Calicivirus]	ATCC VR-782
*Avian Influenza A	ATCC VR-2072
*Influenza A [VR-544, Hong Kong strain]	ATCC VR-544
*Rhinovirus [R37 VR-1147, Strain 151-1]	ATCC VR-1147
*Polio Type 2, [VR-1002, Lansing Strain]	ATCC VR-1002

]



NOTE: [Bracketed] text is optional wording ***Bold/italicized test is information only and not part of the label.***

Safety Data Sheet

SECTION 1 -- IDENTIFICATION

Product Name: **AXENOHL**

Issue Date: 01/09/2015

Date Revised: NA

Distributed By:
PURE Bioscience, Inc.
1725 Gillespie Way
El Cajon, CA 92020
Telephone: 619-596-8600
Email: technicalinfo@purebio.com

www.purebio.com

Recommended Uses: Concentrated antimicrobial agent. **EPA Reg. No.:** 72977-1

In Case of Emergency: Have the product container or label with you when calling a poison control center or doctor. You may contact CHEMTREC 1-800-424-9300 for emergency medical treatment information.

SECTION 2 -- HAZARDS IDENTIFICATION

GHS Classification – Eye Damage/Irritation Category 2B

Signal Word: Warning

Hazard Statement: Causes eye irritation

Precautionary Statements: Wash contacted areas of body thoroughly after handling. If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical attention.

SECTION 3 -- COMPOSITION / INFORMATION ON INGREDIENTS

Components: **The specific chemical identities and exact percentages (concentrations) of composition have been withheld as a trade secret.**

None of the ingredients is considered hazardous according to the criteria of 29CFR1910.1200 and DOT Reg 49 CFR 172. Ingredients are listed for informational purposes to assist emergency medical response personnel.	**Wt%**
Water (CAS No. 7732-18-5)	> 76
Citric Acid (CAS No. 77-92-9)	< 22
Silver Ions	0.24

SECTION 4 -- FIRST-AID MEASURES

Eye Contact: Hold eyelids open and flush thoroughly with a steady, gentle stream of water for at least 15 minutes. If irritation persists consult a physician.

Skin Contact: Rinse with water. If irritation persists consult a physician.

Inhalation: If breathing is affected, remove victim to fresh air and consult a physician.

Ingestion: If irritation or discomfort occurs, call a physician. DO NOT INDUCE VOMITING.

SECTION 5 -- FIRE-FIGHTING MEASURES

Flammability: Not flammable or combustible.

Flammable Limits: Not applicable.

Extinguishing Media: Not applicable.

Fire and Explosion Hazards: None.

SECTION 6 -- ACCIDENTAL RELEASE MEASURES

Response to Spills: SMALL SPILLS: Contain spill, flush to sanitary sewer, and rinse area with water. LARGE SPILLS: Dike or dam spill, pump to containers or soak up with inert absorbent, and prevent runoff to creeks and waterways. Personal Protective Equipment is not normally required. If contact is likely or for prolonged or repeated contact with concentrate, eye and hand protection is recommended.

SECTION 7 -- HANDLING AND STORAGE

Handling Precautions: Close container tightly when not in use. After dilution, rinse hands and measuring containers with water.

Storage Precautions: Store concentrate in a cool, dry place. Do not contaminate food, feed, or drinking water with concentrate. Keep concentrate from freezing. Keep concentrate out of direct sunlight.

SECTION 8 -- EXPOSURE CONTROLS / PERSONAL PROTECTION

No special protection or precautions have been identified for using this product under directed consumer use conditions. The following recommendations are given for production facilities and for other conditions and situations where there is increased potential for accidental, large-scale or prolonged exposure.

Hygienic Practices:	During dilution, avoid eye and skin contact. If contact occurs, flush thoroughly with water.
Engineering Controls:	It is suggested that an eyewash station be placed near the location where the concentrate is diluted.
Personal Protective Equipment:	Not normally required. If contact is likely or for prolonged or repeated contact with concentrate, eye and hand protection is recommended.

SECTION 9 -- PHYSICAL AND CHEMICAL PROPERTIES

Appearance..... Clear, Colorless liquid
Odor..... Practically Odorless
pH.....1.4 – 1.6
Specific Gravity (H_2O=1).....1.09
Solubility.....Water soluble
VOC Content (% Wt.).....0.00% (0.000 lbs/gallon)

Boiling Point..... Not established
Freezing Point..... Not established
Evaporation Rate (Butyl Acetate=1)..... Not established
Vapor Density (Air=1)..... Not established
Vapor Pressure (mmHg)..... Not established

SECTION 10 -- STABILITY AND REACTIVITY

Chemical Stability:	Stable.
Incompatibility:	May be slightly incompatible with aluminum and copper metals after prolonged exposure. Product IS compatible with most metals including stainless steels.
Hazardous Decomposition:	None.
Polymerization:	None.
Conditions to Avoid:	Not applicable.

SECTION 11 -- TOXICOLOGICAL INFORMATION

THIS PRODUCT DOES NOT CONTAIN ANY KNOWN OR ANTICIPATED CARCINOGENS ACCORDING TO THE CRITERIA OF THE NTP ANNUAL REPORT ON CARCINOGENS, OSHA 29 CFR 1910.1000, SUBPART Z, OR THE IARC MONOGRAPHS.

Acute Oral, Rat ..... LD50>5000 mg/Kg
Acute Dermal, Rat ..... LD50>5000 mg/Kg
Primary Eye Irritation ..... Rabbit – Slightly Irritating

Epidemiology ..... None Known
Teratogenicity ..... None Known
Neurotoxicity ..... None Known
Dermal Sensitization..... Guinea Pigs – Not a contact sensitizer

Subchronic/Chronic Toxicity: Does not contain any recognized carcinogens, mutagens or reproductive toxicants.

SECTION 12 -- ECOLOGICAL INFORMATION

Ecotoxicity:	None.
Environmental Fate:	Readily degraded. Ionic silver is degraded into inert elemental silver or insoluble silver complexes in the environment.

SECTION 13 -- DISPOSAL CONSIDERATIONS

Waste Disposal Method:	Dispose of in accordance with local, state, and federal regulations.
RCRA Classification:	Non-hazardous.

SECTION 14 -- TRANSPORT INFORMATION

DOT Classification:	Non-hazardous.
Exceptions:	None.
Description:	Not applicable.

SECTION 15 -- REGULATORY INFORMATION

TSCA:	TSCA Inventory: All components are listed. TSCA Health and Safety Reporting List: None of the components are listed. TSCA Chemical Test Rules: None of the components are listed. TSCA Section 12b: None of the components are listed. TSCA Significant New Use Rule: None of the components has a SNUR.
CERCLA:	No RQ was assigned to silver compounds. See 50FR13456 (April 4, 1985).
ARA 302/304:	None of the components has a RQ or a TPQ.
SARA 311/312:	None of the components are reportable.
Clean Air:	None of the components are a Hazardous Air Pollutant, Class 1 Ozone Depletor, or Class 2 Ozone Depleter.
Clean Water Act:	None of the components are a Hazardous Substance, Priority Pollutant, or Toxic Pollutant.
OSHA:	None of the components are considered hazardous.
California Proposition 65:	None of the components are listed.

SECTION 16 -- OTHER INFORMATION

ID:	M5060A
Issue Date (Rev):	January 9, 2015

Revision Summary: NA

Safety Data Sheet

SECTION 1 -- IDENTIFICATION

Product Name: **PURE Hard Surface**

Issue Date: 01/09/2015

Date Revised: NA

Distributed By:
PURE Bioscience, Inc.
1725 Gillespie Way
El Cajon, CA 92020
Telephone: 619-596-8600
Email: technicalinfo@purebio.com

www.purebio.com

Recommended Uses: Ready To Use Hard Surface Disinfectant and Food Contact Surface Sanitizer.

In Case of Emergency: Have the product container or label with you when calling a poison control center or doctor. You may contact CHEMTREC 1-800-424-9300 for emergency medical treatment information.

SECTION 2 -- HAZARDS IDENTIFICATION

GHS Classification – Not Classified

Unclassified Hazards: May cause slight eye irritation
Precautionary Statements: Avoid direct skin and eye contact. If in eyes: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: Get medical attention.

HMIS Rating

Health	0
Flammability	0
Reactivity	0

SECTION 3 -- COMPOSITION / INFORMATION ON INGREDIENTS

Components: **The specific chemical identities and exact percentages (concentrations) of composition have been withheld as a trade secret.**

None of the ingredients is considered hazardous according to the criteria of 29CFR1910.1200 and DOT Reg 49 CFR 172. Ingredients are listed for informational purposes to assist emergency medical response personnel.	**Wt%**
Water (CAS No. 7732-18-5)	> 95
Citric Acid (CAS No. 77-92-9)	< 5.0
Silver Ions	0.0030

SECTION 4 -- FIRST-AID MEASURES

Eye Contact: Hold eyelids open and flush thoroughly with a steady, gentle stream of water for at least 15 minutes. If irritation persists consult a physician.
Skin Contact: Rinse with water. If irritation persists consult a physician.
Inhalation: If breathing is affected, remove victim to fresh air and consult a physician.
Ingestion: If irritation or discomfort occurs, call a physician. DO NOT INDUCE VOMITING.

SECTION 5 -- FIRE-FIGHTING MEASURES

Flammability: Not flammable or combustible.

Flammable Limits: Not applicable.

Extinguishing Media: Not applicable.

Fire and Explosion Hazards: None.

SECTION 6 -- ACCIDENTAL RELEASE MEASURES

Response to Spills: SMALL SPILLS: Contain spill, flush to sanitary sewer, and rinse area with water. LARGE SPILLS: Dike or dam spill, pump to containers or soak up with inert absorbent, and prevent runoff to creeks and waterways. Personal Protective Equipment is not normally required. Avoid contact with eyes.

SECTION 7 -- HANDLING AND STORAGE

Handling Precautions: Close container tightly when not in use.

Storage Precautions: Store in a cool, dry place. Do not contaminate food, feed, or drinking water. Keep from freezing. Keep out of direct sunlight.

SECTION 8 -- EXPOSURE CONTROLS / PERSONAL PROTECTION

No special protection or precautions have been identified for using this product under directed consumer use conditions. The following recommendations are given for production facilities and for other conditions and situations where there is increased potential for accidental, large-scale or prolonged exposure.

Hygienic Practices: Avoid direct eye and skin contact. If irritation occurs, flush thoroughly with water. When product is applied to a floor surface, signage should be used to indicate slippery areas until they are dry.

Engineering Controls: Use general ventilation to minimize exposure to mist. Eyewash station is suggested.

Personal Protective Equipment: Not normally required. If contact is likely for prolonged or repeated contact, eye and hand protection is recommended.

SECTION 9 -- PHYSICAL AND CHEMICAL PROPERTIES

Appearance.....Colorless liquid
Odor ..... Practically Odorless
pH 2
Specific Gravity (H_2O=1) ..... Similar to water
Solubility.....Water soluble
VOC Content (% Wt.)..... 0.00% (0.000 lbs/gallon)

Boiling Point..... Not established
Freezing Point ..... Not established
Evaporation Rate (Butyl Acetate=1) ..... Not established
Vapor Density (Air=1)..... Not established
Vapor Pressure (mmHg)..... Not established

SECTION 10 -- STABILITY AND REACTIVITY

Chemical Stability:	Stable.
Incompatibility:	Not applicable.
Hazardous Decomposition:	None.
Polymerization:	None.
Conditions to Avoid:	Not applicable.

SECTION 11 -- TOXICOLOGICAL INFORMATION

THIS PRODUCT DOES NOT CONTAIN ANY KNOWN OR ANTICIPATED CARCINOGENS ACCORDING TO THE CRITERIA OF THE NTP ANNUAL REPORT ON CARCINOGENS, OSHA 29 CFR 1910.1000, SUBPART Z, OR THE IARC MONOGRAPHS.

Acute Oral, Rat .....LD50>5000 mg/Kg
Acute Dermal, Rat .....LD50>5000 mg/Kg
Primary Eye Irritation .....Rabbit – Category IV
Primary Eye Irritation .....Rabbit – Slightly Irritating

Epidemiology ..... None Known
Teratogenicity ..... None Known
Neurotoxicity ..... None Known
Dermal Sensitization..... Guinea Pigs – Not a contact sensitizer

Subchronic/Chronic Toxicity: Does not contain any recognized carcinogens, mutagens or reproductive toxicants.

SECTION 12 -- ECOLOGICAL INFORMATION

Ecotoxicity:	None.
Environmental Fate:	Readily degraded. Ionic silver is degraded into inert elemental silver or insoluble silver complexes in the environment.

SECTION 13 -- DISPOSAL CONSIDERATIONS

Waste Disposal Method:	Dispose of in accordance with local, state, and federal regulations.
RCRA Classification:	Non-hazardous.

SECTION 14 -- TRANSPORT INFORMATION

DOT Classification:	Non-hazardous.
Exceptions:	None.
Description:	Not applicable.

SECTION 15 -- REGULATORY INFORMATION

TSCA:	TSCA Inventory: All components are listed. TSCA Health and Safety Reporting List: None of the components are listed. TSCA Chemical Test Rules: None of the components are listed. TSCA Section 12b: None of the components are listed. TSCA Significant New Use Rule: None of the components has a SNUR.
CERCLA:	No RQ was assigned to silver compounds. See 50FR13456 (April 4, 1985).
ARA 302/304:	None of the components has a RQ or a TPQ.
SARA 311/312:	None of the components are reportable.
Clean Air:	None of the components are a Hazardous Air Pollutant, Class 1 Ozone Depletor, or Class 2 Ozone Depleter.
Clean Water Act:	None of the components are a Hazardous Substance, Priority Pollutant, or Toxic Pollutant.
OSHA:	None of the components are considered hazardous.
California Proposition 65:	None of the components are listed.

SECTION 16 -- OTHER INFORMATION

ID:	M5141
Issue Date (Rev):	01/09/2015

Revision Summary: NA

SPECIFICATION

Specification for **Silver dihydrogen citrate (SDC) - Tradename: Axenohl**
Manufactured by: ETI H2O, a division of PURE Bioscience

Parameter	Method	Target	Range
Silver Content	ICP or ISE	2400 ppm	2160 - 2640
Citric acid Content	HPLC or Titration	20.00%	19-22%
Water Content	Weight	79.76%	77.7-80.8%
Color	Visual Test	Colorless	Conforms
Odor	Organoleptic	Odorless	Conforms
Appearance	Visual Test	Simuilar to Water	Conforms

1725 Gillespie Way El Cajon CA 92020
telephone: 619-596-8600 facsimile: 619-596-8790

SPECIFICATION

Product Name: PURE Hard Surface (EPA Reg. No. 72977-5-73912/ SDC3A EPA Reg. No. 72977-5)
Manufactured for: PURE Bioscience, Inc.

Parameter	Method	Target	Range
Silver Content	ICP or ISE	30 ppm	27 - 33 ppm
Citric acid Content	HPLC or Titration	4.846%	4.6037 - 5.0883%
Color	Visual Test	Colorless	Conforms
Odor	Organoleptic	Odorless	Conforms
Appearance	Visual Test	Clear liquid	Conforms

1725 Gillespie Way El Cajon CA 92020
telephone: 619-596-8600 facsimile: 619-596-8790

Attachment 4

FOREWORD INTRODUCTION

CITRIC ACID

CAS N°:77–92–9

SIDS Initial Assessment Report

for

11th SIAM

(Orlando, Fla., January 2001)

Chemical Name:	Citric acid
CAS No.:	77–92–9
Sponsor Country:	Switzerland
National SIDS Contact Point in Sponsor Country:	Dr Georg Karlaganis Swiss Agency for the Environment, Forests and Landscape CH–3003 Berne, Switzerland georg.karlaganis@buwal.admin.ch

HISTORY:

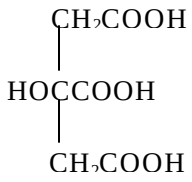
The chemical was chosen by the Sponsor Company and the Swiss authorities in the frame of the ICCA Initiative.

no testing (X)
testing ( )

COMMENTS:

Deadline for Circulation:	10 November 2000
Date of Circulation:	10 November 2000

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-92-9
Chemical Name	Citric acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Based on many experimental data in animals and on human experience, citric acid is of low acute toxicity. The NOAEL for repeated dose toxicity for rats is 1200 mg/kg/d. The major, reversible (sub)chronic toxic effects seem to be limited to changes in blood chemistry and metal absorption/excretion kinetics. Citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. The NOAEL for reproductive toxicity for rats is 2500 mg/kg/d. Further, it is not mutagenic *in vitro* and *in vivo.* Also, the sensitising potential is seen as low. In contrast, irritation, in particular of the eyes but also of the respiratory pathways and the skin, is the major toxicological hazard presented by citric acid; this conclusion is confirmed by a series of reports relating to eye and skin irritation.

Environment

Due to its physico-chemical characteristics citric acid is highly mobile in the environment and will partition to the aquatic compartment. Citric acid is rapidly degraded in both sewage works and surface waters and in soil. Citric acid is of low acute toxicity to freshwater fish, daphnia and algae and also to the few marine species tested; longer-term tests show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria including activated sludge micro-organisms. Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

Exposure

Citric acid is a water soluble organic solid. It is a natural substance that appears as an intermediate in the basic physiological citric acid or Krebs cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes, current global production is estimated to approach 1,000,000 t/a. It has wide dispersive use, being added to processed food and beverages, used in pharmaceutical preparations and in household cleaners as well as in special technical applications.

A large body of physico-chemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old and some located only in standard reference works and reviews. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended.

Full SIDS Summary

CAS No. 77–92–9		Species	Protocol	Results
Physical-Chemical				
2.1	Melting Point		NA	152–159 °C
			NA	~153 °C
2.2	Boiling Point			none; decomposition > 175 °C
2.3	Relative Density		NA	1.665 at 20 °C
2.4	Vapour Pressure			no studies located
			calculated	7.3×10^{-7} Pa (25 °C)
2.5	Partition Coefficient		NA	logPow = –1.72 at 20 °C
2.6	Water solubility		NA	576–771 g/l at 20 °C/room temperature, data from 4 sources
			NA	1330 g/l, "cold water"
	*p*H Value		NA	2.2 at 0.1 *N*
			NA	~1.8 at 50 g/l and 25 °C
	Dissociation Constants		NA	$pKa_1 = 3.13$, $pKa_2 = 4.76$, $pKa_3 = 6.4$
2.11	Oxidation/Reduction Potential			no studies located
2.12	Additional Data: Henry's Law Constant		calculated	$K_H = 2.3 \times 10^{-7}$ Pam^3/mol
Environmental Fate and				
3.1.1	Photodegradation			no studies located
			calculated	$t_{½}$ = 2.3 days in the atmosphere
3.1.2	Stability in Water		calculated	$t_{½}$ = 72.9 years at *p*H 1, stable
3.1.3	Stability in Soil		NA	"substantial disappearance of citrate from soil within 7 days"
3.2	Monitoring Data		background concentration measurement	<0.04–0.2 mg/l, river surface water 0.025–0.145 mg/l, Atlantic coast seawater
3.3.1	Transport			no studies located
3.3.2	Distribution		calculated: fugacity level III (dynamic)	emission 33% each to water, soil and air: 55.76% to water, 44.2% to soil, 0.02% to sediment, 0.02% to air
			calculated: fugacity level I (static)	static equilibrium concentrations: 99.99% to water, <0.01% to soil, <0.01% to sediment, <0.01% to air
3.4	Mode of Degradation in Actual Use		NA	synthesised and metabolised by all eukaryote cells in the Krebs cycle; easily oxidised by common oxidising agents
3.5	Biodegradation		Modified Sturm test	97% (CO_2 evolution), readily biodegradable
			Closed Bottle test	BOD_{30}/COD = 90%, readily biodegradable
			Closed Bottle test	BOD_5 = 526 mg, COD = 728 mg, BOD_5/COD = 0.72, readily
			Closed Bottle test	BOD_5/ThOD = 58%–61% (3 publications), readily
			Closed Bottle test	BOD_1/ThOD = 13%
			Closed Bottle test	BOD_{20}/ThOD = 98%, readily biodegradable

CAS No. 77–92–9		Species	Protocol	Results
			Zahn-Wellens test	85%, 1 day 98%, 7 days; inherently biodegradable
			Coupled Units test	93% (COD removal), ultimately biodegradable
Ecotoxicology				
4.1	Acute/Prolonged Toxicity to Fish	*Carassius auratus*	NA	LC_0 = 625 mg/l, LC_{100} = 894 mg/l, "long-time exposure in hard water"
		Lepomis macrochirus	NA	LC_{50} = 1516 mg/l, 96 h
		Leuciscus idus	NA	LC_{50} = 440–760 mg/l, 96 h, "solution was not neutralised"
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	NA	EC_0 = 80 mg/l, EC_{100} = 120 mg/l, "long-time exposure in soft water"
		Daphnia magna	NA	EC_0 = 1206 mg/l, EC_{50} = 1535 mg/l, EC_{100} = 2083 mg/l (neutralised) EC_0 = 73 mg/l, EC_{50} = 85 mg/l, EC_{100} = 98 mg/l (not neutralised)
		Carcinus maenas (crab)	NA	LC_{50} = 160 mg/l, 48 h
4.3	Toxicity to Aquatic Plants, eg Algae	*Scenedesmus quadricauda*	NA	EC_0 = 640 mg/l, 7 days
		Pavlova lutheri (saltwater	NA	TLC (7d) = 1 – 300 mg/l
		Chaetoceros gracilis	NA	TLC (7d) = 1 – 300 mg/l
4.4	Toxicity to Micro-organisms, eg Bacteria	*Microcystis aeruginosa*	NA	EC_0 = 80 mg/l, 8 days
		Nitrosomonas sp.	NA	no inhibition on NH_3 oxidation at 100 mg/l
		Pseudomonas putida	NA	EC_0 > 10,000 mg/l, 16 h
		37 strains of acidophilic bacteria	NA	positive growth on all strains with 500 mg citric acid/l as sole C source for 30 days at *p*H 3
		Arthrobacter globiformis, 10 strains	NA	good degradation of citric acid as sole C source over 5 days
		Entosiphon sulcatum	NA	EC_0 = 485 mg/l, 72 h
		Tetraselmis tetrathele (saltwater)	NA	TLC (7d) = 1 – 300 mg/l
		Tetramitus rostratus (freshwater)	NA	TLC (35hrs) ≤ 108 mg/l
		Uronema parduzci	NA	TLC = 622 mg/l
4.5.1	Chronic Toxicity to Fish	*Carassius auratus*	NA	LC_0 = 625 mg/l, LC_{100} = 894 mg/l, "long-time exposure in hard water"
4.5.2	Chronic Toxicity to Aquatic Invertebrates	*Daphnia magna*	NA	EC_0 = 80 mg/l, EC_{100} = 120 mg/l, "long-time exposure in soft water"

CAS No. 77–92–9		Species	Protocol	Results
4.6.1	Toxicity to Soil-Dwelling Organisms			no studies located
4.6.2	Toxicity to Terrestrial Plants			all plants produce citric acid
4.6.3	Toxicity to Other Non-Mamm. Terrestrial			no studies located
4.8	Biotransformation and Kinetics			citric acid is an intermediate in the Krebs cycle which takes place in every eukaryote cell
4.9	Additional Remarks			citric acid is “extremely widespread in nature”
				citric acid is “widely distributed in plants and animal tissues and fluids”
				in man, during 24 h approximately 2000 g of citric acid are formed and further metabolised as intermediates of the Krebs cycle in adults
Toxicity				
5.1.1	Acute Oral Toxicity	rat	NA	LD_{50} = 3,000 mg/kg
		rat	NA	LD_{50} = 5,000 mg/kg
		rat	NA	$LD_{50} \geq$ 6,730 mg/kg
		rat	NA	LD_{50} = 12,000 mg/kg
		mouse	NA	LD_{50} = 5,400 mg/kg for males and females; 5 males, 5 females, gavage, 5 concentrations in water, controls
		rabbit	NA	lethal dose = 7,000 mg/kg (probably lowest lethal dose)
5.1.2	Acute Inhalation Toxicity			no studies located
5.1.3	Acute Dermal Toxicity			no studies located
5.1.4	Acute Toxicity, Other Routes	rat	NA	LD_{50} = 5,500 mg/kg by s.c. application
		mouse	NA	LD_{50} = 2,700 mg/kg by s.c. application
5.2.1	Skin Irritation	rabbit	NA	dose = 500 mg/24 h; slightly irritating, effects reported as “mild”
		rabbit	OECD 404	according to guideline; slightly irritating, avg. erythema score = 0.33, oedema = 0
		rabbit	Draize test	0.5 ml of 30% aq. solution for 4 h under occlusive patch produced no effect in intact skin, slight to well defined effect in abraded skin; prim. irritation index = 0.84
		man	clinical report	irritant skin dermatitis in waiters and bakers attributed to citric acid
		man	clinical report	in solution the acid may produce pain if applied to abraded skin
		man	clinical report	a 0.3 *N* solution (~2%) can “sting” intact skin
		man	clinical report	patch testing of 60 eczema patients with 2.5% citric acid in petrolatum (probably 24-h covered contact) did not produce any irritant reactions

CAS No. 77–92–9		Species	Protocol	Results
5.2.2	Eye Irritation	rabbit	NA	irrigation for 30 min with 0.5% or 2% aq. solution caused permanent cloudiness resp. severe dense opacification
		rabbit	NA	750 µg for 24 h caused “severe” effects
		rabbit	OECD 405	according to guideline; avg. cornea score = 2.8; iris = 0.0; conjunctiva = 1.7
CAS No. 77–92–9		**Species**	**Protocol**	**Results**
		rabbit	Draize test	0.1 ml of 10% or 30% aq. solution placed in lower conjunctival sac of 3 animals for 1 s; 10% sol. caused moderate to weak conjunctival irritation for 1 week, avg. Draize score = 9.3; 30% sol. caused well-defined to moderate conjunctival irritation in 2/3 animals for 14 d plus short-lasting superficial lesion of conjunct. epithelium, avg. Draize score =16.0
		man	clinical report	severe eye damage in a man splashed in the eye with saturated aq. solution
5.3	Sensitization	man	clinical report	mouth sores, headache, asthma, nasal blockage, general tiredness. itchiness were reported after the ingestion of foods containinng citric acid
		man	clinical report	citric acid might be a skin sensitizer
5.4	Repeated Dose Toxicity	rat	internal test F. Hoffmann-La Roche Ltd	NOEL = 4,000 mg/kg/d, LD_{50} = 5,600 ± 440mg/kg/d; oral, gavage, once daily for 5 days, post-exposure observation 10 days; 10 males, 10 females, avg. weight = 150 g
		rat	NA	oral, dietary, feed containing 1.2% citric acid, probably ad libitum, for 90 weeks; “...no harmful effects on the growth of two successive generations. No effect on reproduction, blood characteristics, pathology ..., although a slight increase in dental attrition was reported”.
		rat	NA	oral, dietary, feed containing 5% and 3% citric acid for 2 years, slightly decreased growth was observed but no tissue abnormalities were found on examination of the major organs. NOAEL = 1200 mg/kg/d
		rat	NA	oral, dietary, feed containing 1.2, 2.4, 4.8% citric acid for 6 weeks. At the top dose, slight growth reduction, mild blood and urine changes and slight degeneration of the thymus gland and the spleen were observed.

CAS No. 77–92–9		Species	Protocol	Results
		rat	NA	oral, dietary, feed containing 2% citric acid. The absorption and urinary excretion of calcium and magnesium were unaffected, although urinary zinc excretion was temporarily elevated.
		rat	NA	oral, dietary, feed containing 1.2% citric acid for 1 year. No adverse effect were reported (with the possible exception of slight changes in tooth structure) in two successive generations.
		mouse	NA	oral, dietary, feed containing 5% citric acid, probably ad libitum, for unspecified period to male mice; decreased growth and lower survival times in treatment group 11-12 months as opposed to 16-17 months in controls.
		rabbit	NA	oral, dietary, feed containing 7.7% sodium citrate, probably ad libitum, for 150 days to 15 rabbits; no adverse effects were reported
		dog	NA	oral, dietary, fed 1.38 g citric acid/kg bw daily to 3 dogs for up to 120 days; no adverse effects were reported
		guinea pig	NA	oral, dietary supplement with 1–5% citric acid to unknown number of animals for up to 60 days; reduced packed blood cell volume, no histology was performed
		pig	NA	oral, dietary; young pigs fed cadmium-enriched diet containing 5% citric acid; only reported effects were elevated Cd levels in liver and kidneys and decreased zinc level in muscle
		sheep	NA	6 sheep given 795 mg citric acid/kg bw daily via ruminal cannula for uspecified time; no adverse effects were reported
5.5.A	Genetic Toxicity *in vitro*, Bacterial Test	*Salmonella typhimurium*	OECD 471	not mutagenic in 4 defined strains with and without metabolic activation
		Salmonella typhimurium	OECD 471	not mutagenic in 5 defined strains with and without metabolic activation
5.5.B	Genetic Toxicity *in vitro*, Non-Bacterial Test	yeast	"yeast gene mutation assay"	not mutagenic with and without metabolic activation
		Chinese hamster	NA	no clastogenic effects reported in fibroblast culture cells at concentrations up to 1 mg citric acid/ml
5.6	Genetic Toxicity *in vivo*	rat	dominant lethal assay	no mutagenic potential after doses of 3 g/kg (possibly per day) for 5 days
		rat	NA	no chromosomal damage in bone marrow of rats fed up to 3 g/kg/d for 5 days

CAS No. 77–92–9		Species	Protocol	Results
5.8	Toxicity to Reproduction	rat	NA	2-generation study over 90 weeks, oral, dietary, feed containing 1.2% (w/w) citric acid; no harmful effects on growth of two successive generations nor on reproduction parameters, pathology, blood characteristics or calcium levels, only slight dental attrition was reported
		rat	NA	oral, dietary, feed containing 1.2% citric acid plus 0.1% sodium citrate for 29 weeks prior to mating and then for "another few months"; no harmful effects reported
		rat	NA	oral, dietary, feed containing 5% citric acid to female rats prior, during and subsequent to mating; no harmful effects reported NOEL = 2500 mg/kg/d
		rat	NA	oral, 295 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no teratogenic or harmful effects reported
		rat	NA	oral, 241 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no teratogenic or harmful effects reported
		mouse	NA	oral, dietary, feed containing 5% citric acid to female mice prior, during and subsequent to mating; litter size and survival of offspring were unaffected NOEL = 7500 mg/kg/d
		rabbit	NA	up to 425 mg citric acid/kg given to female rabbits during days 6–18 of pregnancy; no teratogenic or harmful effects reported NOEL = 425 mg/kg/d
		hamster	NA	up to 272 mg citric acid/kg given to female hamsters during days 6–10 of pregnancy; no teratogenic or harmful effects reported
5.9	Developmental Toxicity/ Teratogenicity	rat	NA	oral, > 241 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no indication of adverse effects on nidation, foetal survival or abnormalities
		rats and mice	NA	oral, diet, feed contianing 5% citric acid given for unspecified time; no negative effect on litter size or subrvival up to weaning of pups
5.10	Other relevant information	rats, mice, rabbits	NA	citric acid and its salts injected by various routes caused nervous system, lung, spleen and liver effects
		rat	NA	intravenous infusion with sodium citrate solution was shown to increase calcium excretion

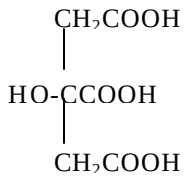
CAS No. 77–92–9		Species	Protocol	Results
		horse	NA	intravenous injection with 0.56 mg sodium citrate/kg bw did not cause any cardiovascular effects or effects on blood composition
		rats, mice, rabbits	NA	Severe damage to the stomach lining and nervous system effects were reported with high doses of citric acid
				citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological avilability of iron and calcium
				it has been shown in an in vitro system for the development of artificial caries that the application of citric acid to teeth may make them more susceptible to decay
				citric acid and its salts may increase the absorption and retention of ingested metals such as aluminium, tin, cadmium and lead
		dog	NA	severe ulceration and tissue damage occured in dogs receiving tongue application of 0.1 ml of 50% citric acid solution for 5 minutes
		dog	NA	broncvhoconstriction was induced with citric acid
		guinea-pigs	NA	Coughing was reported when guinea-pigs were exposed for 30 minutes to atmospheric citric acid concentration of 81 mg/m^3
		man		the lowest concentration of inhaled citric acid required to produce involuntary coughing ranged from 0.5 to 32 mg/ml
5.11	Experience with Human Exposure		reference book	total daily consumption of citric acid from natural sources and food additives may exceed 500 mg/kg
			clinical report	after ingesting a single dose of 25 g citric acid (approx. 417 mg/kg) a young woman vomited and almost died
			clinical report, various sources	systemic effects after single exposure through i.v. transfusion of large amounts of citrated blood: depletion of body calcium, effetcs on blood composition, nausea, exacerbation, muscle weakness, breathing difficulties up to cardiac arrest

CAS No. 77–92–9		Species	Protocol	Results
			clinical report, various sources	systemic effects after repeated exposure through oral doses of potassium citrate, either solid or dissolved in water: minor gastrointestinal disturbances, diarrhoea, indigestion, nausea, “burning”
			textbook	potassium and sodium citrate have been used in doses of up to 15 g/d as medications presumably without any marked side effects
			reference book	excretion of citric acid in 82 adults ranges from 1.5 to 3.68 mmol/d (total range 0.4–8.80 mmol/d) respectively from 290 to 707 mg/d (total range 80–1,690 mg/d)

NA = Not available; most of these data are from widely accepted, peer-reviewed secondary sources.

SIDS Initial Assessment Report

1. IDENTITY

Name	Citric acid
CAS No.	77–92–9
Chemical Name	2-Hydroxy-1,2,3-propanetricarboxylic acid
Synonyms	β-Hydroxytricarballylic acid 2-Hydroxypropanetricarboxylic acid
Structure	
Empirical Formula	$C_6H_8O_7$
Molecular Weight	192.12 g/mol
Purity	> 99 % w/w
Melting Point	~153 °C
Boiling Point	not applicable, decomposition above 175 °C
Water Solubility	≥ 576 g/l (20 °C)
Dissociation constants	pKa_1 = 3.13, pKa_2 = 4.76, pKa_3 = 6.4 (25 °C)
n-Octanol/water partition coefficient	log P_{OW} = –1.72 (20 °C)
Vapour Pressure	known to be nonvolatile; no precise data located QSAR estimation: 7.3 x 10^{-7} Pa at 25 °C
Classification	classified as irritating to eyes

Citric acid is a water soluble organic solid with a melting point of approximately 153 °C. It is an ubiquitous natural substance that appears as an intermediate in the basic physiological citric acid cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes and added to processed food and beverages, used in pharmaceutical preparations and in household cleaners as well as in special technical applications.

2. EXPOSURE

2.1 General Discussion

Between 100,000 and 500,0000 tonnes/annum of citric acid is estimated to have been produced in Europe, including Eastern Europe and Israel, in 1999. Global production is estimated by industry to be approaching 1,000,000 t/a. Worldwide, citric acid production is mainly through microbiological fermentation of molasses and sugar solutions, while extraction from lemon juice or chemical synthesis is negligible. Dilute citric acid from filtered fermentation broths is precipitated with milk of lime (calcium hydroxide) as practically insoluble calcium citrate, which is then reacted with sulfuric acid to form citric acid and calcium sulfate (gypsum) as a recoverable and valorisable by-product.

Approximately 50% of the production is estimated to be used by the beverage and soft drinks industry, another 20% in food processing industry and around 10% in pharmaceutical industry, where citric acid is used as an acidulant, buffering agent, taste enhancer and synergist in antioxidant mixtures. Thus, approximately four fifths are destined for human consumption and have a very wide dispersive use. The remainder is split between technical applications in various industries as a complex-forming agent, cleaning agent, softening agent, decalcifying agent, derusting agent, corrosive agent and synergist in antioxidant mixtures; many of those applications also have wide dispersive use, eg, washing powders and detergents. Last, small fractions are used in special applications such as citrate buffering of whole blood samples for transfusion.

2.2 Environmental Partitioning and Fate

Citric acid is exceedingly soluble in water, has relatively low acid dissociation constants that ensure that the substance is at least partly deprotonated in aqueous solution at all environmentally relevant pH values. Additionally, it has a low *n*-octanol/water partition coefficient; no precise information was found on vapour pressure but the melting point is around 153 °C. The result of a QSAR estimation is 7.3×10^{-7} Pa at 25 °C. These properties of citric acid indicate that it is likely to partition mainly into the water phase, with very little distributing into the atmosphere. In addition, due to the high water solubility the substance is unlikely to adsorb onto soil or sediment. Using a level III generic fugacity model (see Table 1) it is predicted that if citric acid is released to water, it is unlikely to partition into other environmental compartments. Release of citric acid to air is likely to lead to distribution into soil and water through deposition processes, while release or deposition onto soil is predicted to lead to redistribution into the aquatic compartment. In corroboration of this prediction, a pure equilibrium partitioning model reflecting only distribution based on free intermedia exchange (but neglecting emission, advection or reaction; Mackay *et al.:* EQC Model v. 1.0, Level I, Environmental Modelling Centre, Trent University, Canada) results in the partitioning of 99.99% to the aquatic compartment.

Table 1: Environmental distribution of citric acid using a level III generic fugacity model [Mackay *et al.:* Level III, Fugacity-based Environmental Equilibrium Partitioning Model, v. 2.2, Environmental Modelling Centre, Trent University, Canada].

Compartment	**Release:**			
	100 % to air	100 % to water	100 % to soil	33 % each to air, water and soil
Air	0.06 %	< 0.01 %	< 0.01 %	0.02 %
Water	38.41 %	99.96 %	36.28 %	55.76 %
Sediment	0.01 %	0.04 %	0.01 %	0.02 %
Soil	61.51 %	< 0.01 %	63.70 %	44.20 %

In the aquatic compartment, citric acid may be expected to be rapidly degraded as it is known to be well biodegradable from several ready and inherent aerobic biodegradation tests (Table 2).

Table 2: Biodegradation test data for citric acid.

Test system	**Results**	**Notes**
Modified Sturm Test	97% (CO_2 evolution) 100% (DOC removal)	readily biodegradable; exposure period not stated
Closed Bottle Test	BOD_{30}/COD = 90%	readily biodegradable
BOD_5/COD Ratio	BOD_5= 526 mg COD = 728 mg BOD_5/COD = 0.72	readily biodegradable; concentration of test substance and activated sludge not stated
BOD_5/ThOD Ratio	BOD_5/ThOD = 58%–61%	readily biodegradable; data from three publications
BOD_1/ThOD Ratio	BOD_1/ThOD = 13%	
BOD_{20}/ThOD Ratio	BOD_{20}/ThOD = 98%	readily biodegradable; initial test substance concentration 720 mg/l
Zahn-Wellens Test	85%, 1 day (DOC removal)	inherently biodegradable
Zahn-Wellens Test	98%, 7 days (DOC removal)	inherently biodegradable
Coupled Units Test	93% (COD removal)	ultimately biodegradable; exposure period not stated

The prediction of extensive and rapid degradation, both in sewage treatment plants and in natural water bodies, is borne out by experimental data confirming double to three times the degradation of low concentrations of citric acid in lake water at *p*H 8 as compared to in distilled water. Monitoring data show that while raw sewage contains up to 10 mg citrate/l, background concentrations in river water range between < 0.04 and maximally 0.2 mg/l, respectively in Atlantic coast surface seawater between 0.025 and 0.145 mg/l. Regarding these surface water concentrations it should be kept in mind that these citrate concentrations do not only derive from manmade citric acid but that citric acid is extremely widespread in nature respectively widely distributed in plants and animal tissues and fluids and that every single eukaryote organism produces citric acid and excretes part of it to the environment.

Estimation of the indirect photolysis using a photochemical hydroxyl radical reaction constant of 7.02 x 10^{-12} cm^3/mol sec and assuming a hydroxyl radical concentration 0.5 x 10^6 OH/cm^3 would result in an atmospheric half life of 2.3 days (Meylan and Howard, Epiwin, SRC).

2.3 Consumer and Occupational Exposure

Industrial releases of citric acid may occur from the sites of production and through use in industrial processes. Consumers are directly exposed to citric acid or its salts in diluted concentrations in many applications from soft drinks and processed food to common household cleaners, detergents, washing powders etc.; there are no acceptable daily intake levels. Occupational exposure may occur during manufacturing and processing of citric acid; there are no recommended occupational exposure levels.

3. HUMAN HEALTH HAZARDS

In human (as well as in animal and plant) physiology, citric acid is a very common intermediate in one of the central biochemical cycles, the Krebs or tricarboxylic acid cycle, which takes place in every cell. It completes the breakdown of pyruvate formed from glucose through glycolysis, thereby liberating carbon dioxide and a further four hydrogen atoms which are picked up by electron transport molecules. Thus, in man approximately 2 kg of citric acid are formed and metabolised every day. This physiological pathway is very well developed and capable of processing very high amounts of citric acid as long as it occurs in low concentrations. Part of the circulating (mainly metabolic but also ingested) citric acid is excreted in urine, with 24-hour urine reference values between 1.5 and 3.68 mmol, corresponding to 0.29–0.71 g citric acid excreted per person per day.

3.1 Acute toxicity

Citric acid has a low acute toxicity by oral application in both rat (LD_{50} = 3,000–12,000 mg/kg, 3 different values) and mouse (LD_{50} = 5,400 mg/kg). General effects comprised physiological disturbances (acidosis and calcium deficiency), while “high” doses caused nervous system effects as well as severe damage to the stomach mucosa.

By subcutaneous application, LD_{50} values of 5,500 mg/kg in rats and 2,700 mg/kg in mice were reported.

Injection of citric acid by various routes in rats, mice and rabbits (no doses stated) caused nervous system, lung, spleen and liver effects that were in part attributed to acidosis and calcium deficiency.

Ingestion of a single dose of 25 g of citric acid by a woman (corresponding to approx. 417 mg/kg) caused vomiting and nearly dying in one reported case. Volunteers given oral doses of potassium or magnesium citrate corresponding to approx. 4.7 g of citric acid did not suffer any overt gastrointestinal effects.

Injection of large volumes of citrated blood during transfusion may lead to hypocalcaemia and changes in blood composition with concomitant nausea, muscle weakness, breathing difficulties and even cardiac arrest.

No animal studies are available for acute dermal and acute inhalation toxicity.

3.2 Irritation and sensitisation

3.2.1 Irritation to the skin

Local effects of citric acid to the skin (rabbit) are reported as slightly irritating in two studies and as not irritaing in a third study using a 30% aqueous solution.

The application of a 50% citric acid solution to the tongue of dogs for 5 minutes resulted in severe ulceration and tissue damage.

3.2.2 Irritation to the eye

Two nonstandard studies on eye irritation using presumably neat citric acid applied for 24 hours respectively a 2% aqueous solution for 30 minutes found severe and permanent injury to rabbit eyes. In a recent study the application of 0.1 ml of a 30% solution of citric acid to one eye for one second resulted in a well-defined to moderate conjunctival irritation which disappeared in two of the three treated rabbits within 14 days; additionally, a short-lasting superficial lesion of the conjunctival epithelium was noted, but no macroscopical alteration of the cornea.

In an acute eye irritation/corrosion test in rabbits according to OECD 405 citric acid was highly irritating.

3.2.3 Irritation to the respiratory tract

Citric acid (concentration and application not stated) caused brochoconstriction in dogs with nonspecific airway hyperreactivity.

Coughing is reported for guinea pigs exposed for 30 minutes to atmospheric citric acid concentrations of 81 mg/m^3 (aerosolised 6% solution). Coughing was also produced in guinea pigs exposed to 75 mg citric acid/ml as an aerosol for 3 minutes.

Coughing was also caused by instillation of 1 ml of an approx. 5.2% solution to the lower trachea in lambs, but not by instillation to the mid-trachea or laryngeal area.

According to current criteria, pure citric acid and aqueous solutions must be judged as irritant to the eyes but not to the skin.

3.2.4 Experience with human exposure

An irritant skin dermatitis attributed to citric acid has been reported amongst waiters and bakers. While presumably aqueous solutions (2% in one case, not stated in the other) may produce pain or “sting”, patch testing of 60 eczema patients with 2.5% citric acid in petrolatum did not produce any irritant or allergic reactions; thus, the reaction appears to reflect mainly the acid effect of the substance, which in unbuffered 2% to 2.5% aqueous solution results in a pH of approximately 2.

Severe eye damage was described in a patient who was splashed in the eye with a saturated solution of citric acid. Mouth ulcers may be provoked by citric acid and inhalation of citric acid aerosols may induce coughing and bronchoconstriction.

Symptoms of possible sensitisation were described in a man after the ingestion of foods containing citric acid; challenge by direct application of citric acid crystals to inside surface of his mouth produced sores, as did some other organic acids, but potassium citrate crystals and magnesium citrate solution did not. In another case, urticaria and mouth ulcers were reported following exposure to citric acid, with no further details given.

A standard textbook implies that citric acid might be a skin sensitizer by recommending patch tests with aqueous solutions to detect sensitised individuals. However, patch testing of 60 eczema patients with 2.5% citric acid in petrolatum did not produce any irritant or allergic reactions. Genuine sensitisation to citric acid seems to be a rare phenomenon.

3.3 Repeated dose toxicity

3.3.1 Animal data

Groups of 10 male and 10 female rats were given 2 g to 16 g/kg/d orally by gavage during 5 days. A NOEL of 4000 mg/kg/d and an LD_{50} of 5600 mg/kg/d were determined.

Groups of 10 male rats being fed up to 4.8% citric acid in feed (corresponding to approx. 4.67 g/kg/d) for 6 weeks showed slight growth reduction and, in the highest-dose group, mild blood and urine parameter changes and slight degeneration of the thymus gland and spleen.

In 9 rats being fed 2% citric acid (approx. 0.13 g/kg/d) no effect on food consumption or body weight was noted nor were the absorption and urinary excretion of calcium and magnesium affected, however, urinary zinc excretion was found to be temporarily elevated.

In male mice being fed 5% citric acid (approx. 7.5 g/kg/d; in the range of published acute LD_{50}) for an unspecified time, decreased growth and lower survival times (11–13 vs. 16–17 months in controls) were reported.

In guinea pigs fed 1–5% citric acid (approx. 0.4–2 g/kg/d) for 60 days, a reduced packed cell volume in the blood was the only effect noted.

No adverse effects were seen in both rabbits and dogs fed approx. 1.5 resp. 1.4 g/kg/d for 150 resp. 120 days.

Body weight gain was unaffected in young pigs fed a cadmium-enriched diet containing 5% citric acid (approx. 4 g/kg/d), but elevated cadmium in the liver and kidneys and decreased zinc levels in muscle were found.

A 2-year chronic oral study in rats being given 5% or 3% citric acid in feed (approx. 2 resp. 1.2 g/kg/d) found slightly decreased growth in the higher dosage group but no tissue abnormalities in the major organs. From the lower dosage a NOAEL of 1200 mg/kg/d results. Similarly, NOAELs of 1500 mg/kg/d (rabbit) and of 1400 mg/kg/d (dog) have been determined.

No adverse effects, with the possible exception of slight changes of tooth structure, were found when two successive generations of rats were fed 1.2% citric acid (approx. 600 mg/kg/d; duration not stated, probably about one year).

3.3.2 Human data

Repeated exposure of up to 15 g/d of potassium and sodium citrate as medications did not cause any reported marked side effects, but minor gastrointestinal disturbances (diarrhoea, indigestion, nausea, “burning”) were experienced by 22 out of 81 patients taking potassium citrate in water and 7 out of 75 taking solid potassium citrate (doses not stated in both groups) for the treatment of renal calculi.

Ingestion of potassium citrate solutions, an unknown but large volume on possibly more that on occasion in one case and 200–400 ml over 5–7 days in two other cases, caused abnormal heart rhythms, which were assessed as probably due to elevated potassium levels rather than to citrate.

Daily ingestion of 6 g of sodium citrate in 10% aqueous solution over 4 days in 10 men affected the blood acid-base balance, with the urine becoming more alkaline and sodium excretion being increasing while magnesium and potassium excretion was decreased.

In general, citric acid is a strong chelating agent, the dietary uptake of which may interfere with biological availability, absorption and excretion of metals. Further, loss of superficial enamel and erosion of teeth as well as local irritation result from frequent ingestion of citric acid in beverages including natural fruit juices; citric acid fumes were reported to apparently affect the teeth of exposed workers.

The average daily intake of citric acid from natural sources in the diet and food additives was estimated at about 40 mg/kg for women, 130 mg/kg for infants and 400 mg/kg for individuals on slimming diets; maximum daily intake is reported to reach levels of 500 mg/kg. No formal ADI (acceptable daily intake) level has been specified for citric acid and its common salts by the Joint FAO/WHO Expert Committee on Food Additives nor by the EC Scientific Committee for Food.

3.4 Mutagenicity

In several *in vitro* and *in vivo* tests citric acid was not mutagenic. The substance was not mutagenic either in bacterial tests with *Salmonella typhimurium* (Ames test, 2 studies) and *Escherichia coli,* with and without metabolic activation. Citric acid was shown to reduce the activity of a recognised chemical mutagen in *S. typhimurium.* No clear indication of mutagenicity was reported from studies with *S. typhimurium* or the yeast *Saccharomyces cerevisiae* living in the body cavity of an unspecified laboratory animal nor in *S. cerevisiae* cell cultures with or without metabolic activation. Neither was chromosomal damage caused by citric acid in human and hamster cell cultures.

A dominant lethal assay with male rats being treated with up to 3 g/kg/d for 5 days was negative; no chromosomal damage occurred in the bone marrow cell of these male rats.

3.5 Reproduction and developmental toxicity

In a two-generation 90 days study with male and female rats fed 1.2 % citric acid no adverse effect on reproductive parameters nor any teratogenicity of dietary citric acid was seen. There were no indications of teratogenic or other adverse effects in three shorter-term reproductive studies in rats with dietary dosage of either 5% citric acid (approx. 2.5 g/kg/d) previous, during and after mating (NOEL = 2500 mg/kg/d), or 295 mg/kg/d (route unspecified) during days 6–15 of pregnancy.

Similar findings of no effects were reported for two reproductive and teratogenicity studies in mice receiving either 5 % citric acid (approx. 7.5 g/kg/d; in the range of published acute LD_{50}) previous, during and after mating (NOEL = 7500 mg/kg/d) or 241 mg/kg/d during days 6–15 of pregnancy.

Further, there were no indications of teratogenicity or other adverse effects in female hamsters receiving 272 mg citric acid/kg (presumably daily) during days 6–10 of pregnancy nor in female rabbits receiving up to 425 mg/kg/d during days 6–18 (NOEL = 425 mg/kg/d).

3.6 Carcinogenicity

In a study with only 20 male rats receiving op to 5% citric acid in the feed (approx. 2 g/kg/d) for 2 years no evidence of carcinogenicity was reported.

In a further study with rats fed 1.7% sodium citrate (approx. 0.74 g/kg/d) for 8 weeks no increase in DNA synthesis, a measure of cell proliferation, in the bladder epithelium was found.

In contrast, several nonstandard studies report an increased incidence of tumours in rats treated with known carcinogens and receiving citric acid or citrate (between 1.4 and 2.6 g citric acid equivalents/kg/d for 20–45 weeks) at the same time. In at least one of the studies with sodium citrate in feed and the carcinogen given in drinking water the observed tumorigenic effect was not attributed to the citrate anion but to the sodium cation causing increased water (and thereby carcinogen) intake; in this and another study, citric acid was judged not to have a tumour-promoting effect, respectively not to be a potent tumour promoter.

4. HAZARDS TO THE ENVIRONMENT

Citric acid was tested in many, although often nonstandard ecotoxicity tests that are widely cited in standard works of literature and in reviewed databases. Table 3 lists the results of aquatic tests.

Table 3: Ecotoxicity of citric acid.

Species	Results	Notes
Fish:		
Carassius auratus, goldfish (freshwater)	LC_0 = 625 mg/l LC_{100} = 894 mg/l	"long-time exposure in hard water", exposure period and method not stated
Leuciscus idus, golden orfe (freshwater)	96-h LC_{50} = 440–760 mg/l	"solution was not neutralised", method not stated
Lepomis macrochirus, bluegill (freshwater)	96-h LC_{50} = 1,516 mg/l	method not stated
Crustaceans:		
Daphnia magna (freshwater)	24-h EC_0 = 1,206 mg/l 24-h EC_{50} = 1,535 mg/l 24-h EC_{100} = 2,083 mg/l 24-h EC_0 = 73 mg/l 24-h EC_{50} = 85 mg/l 24-h EC_{100} = 98 mg/l	neutralised not neutralised
Daphnia magna (freshwater)	EC_0 = 80 mg/l EC_{100} = 120 mg/l	"long-time exposure in soft water", exposure period and method not stated
Carcinus maenas (saltwater) (crab)	48-h LC_{50} = 160 mg/l	method not stated
Algae:		
Scenedesmus quadricauda (freshwater green algae)	7-day TLC = 640 mg/l	toxic limit concentration, method not stated
Pavlova lutheri (saltwater chrysophytes)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated
Chaetoceros gracilis, Navicula ramosissima (saltwater diatoms)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated
Protozoa:		
Entosiphon sulcatum (freshwater)	72-h EC_0 = 485 mg/l	method not stated
Tetramitus rostratus (freshwater)	35-h TLC ≤ 108 mg/l	toxic limit concentration, exposure period ambiguous, method not stated
Uronema parduczi (freshwater)	TLC = 622 mg/l	toxic limit concentration, exposure period and method not stated
Tetraselmis tetrathele (saltwater)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated

Bacteria (all freshwater):		
Microcystis	8-day EC_0 = 80 mg/l	cyanobacteria, method not stated
***Nitrosomonas* sp.**	EC_0 = 100 mg/l	no inhibition of nitrification, exposure period and method not
"37 Strains of bacteria"	all strains positive growth 30-day EC_0 = 500 mg/l	microbes isolated from acidic mine water, *p*H = 3, citric acid as sole carbon source, method not stated
Pseudomonas putida	16-h EC_0 > 10,000 mg/l	method not stated
Arthrobacter globiformis, 10 strains	good to excellent degradation	microbes isolated from soil, citric acid as sole C source, mineral salts added, exposure period and method

In freshwater, citric acid appears to be of low toxicity to aquatic acute test standard organisms, fish, daphnia and algae, with consistent LC_{50}/EC_{50} values of several hundred milligrams per litre. Many more results refer to toxic limit concentrations or no effect concentrations, from which no dependable EC_{50} can be derived. In a "long-term" daphnia test in "soft water", which may be assumed not to buffer the acid effect of the test substance, the EC_0 was found to be 80 mg/l and the EC_{100} was 120 mg/l, resulting in a geometric mean EC_{50} of 98 mg/l. Similarly, the lowest reported EC_0 in cyanobacteria was 80 mg/l.

Different strains of bacteria showed positive growth respectively good to excellent degradation with citric acid as the sole carbon source and the same holds for sewage sludge micro-organisms that thrive on citric acid.

The few marine species for which data are available seem to be somewhat more sensitive to citric acid, although at 160 mg/l the only acute LC_{50} reported for a crab is over 100 mg/l, while for two algae and a protozoan the subacute toxic limit concentration is only given as a wide range between 1 and 300 mg/l. Still, at least for the few tested organisms citric acid does not seem to be highly or acutely toxic.

The toxicity of citric acid to other environmentally relevant species has not been determined.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

A large body of physicochemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

5.1.1 Human Health

Based on wide spectrum of data relating to experimental animals and on human experience citric acid has a low acute toxicity; only one case of near fatal human intoxication was found. In a repeated dose study with rats a NOAEL of 1200 mg/kg/d and a LOAEL of 2000 mg/kg/d have been determined. The major subchronic and chronic toxic effects seem to be limited to changes in blood chemistry respectively metal absorption and excretion kinetics, even at high doses. Citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological avilability of iron and calcium. Tooth erosion through dissolution of the enamel due to the acid effect in aqueous solution as well as exposure to citric acid fumes has been reported as a possible adverse consequence of long-term over-exposure to citric acid.

Based on several studies, citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. Further, it is not mutagenic *in vitro* and *in vivo*. Judging from the few reports on intolerance also the sensitising potential of citric acid is seen as low.

Irritation, in particular of the eyes, but also the potential for irritation of the respiratory pathways and the skin is the major, if not the only, genuine toxicological hazard presented by citric acid. This conclusion is borne out by a series of reports relating to eye and skin irritation; further, it is also plausible with regard to the use pattern of citric acid, which must be characterised as ranging from closed to quasi-closed system in manufacturing and processing to wide-dispersive and concerning the whole population in its many final uses.

5.1.2 Environment

Due to its physicochemical characteristics citric acid is highly mobile in the environment and will rapidly partition to the aquatic compartment; distribution to soil is of purely temporary nature, while air or sediment constitute negligible sinks.

Based on several laboratory biodegradation tests (both ready and inherent), one field report in lake water and a few monitoring data, citric acid is rapidly degraded in both sewage works and surface waters. In spite of a genuine high-volume production that has been going on for years, with wide dispersive use pattern, no increase in environmental concentrations has been reported.

Citric acid is of low toxicity to freshwater fish, daphnia and algae; reported EC_{50} values range from just below 100 mg/l to several hundreds of milligrams per litre. LC_{50} values for fish range from 440 to 1516 mg/l. The one marine LC_{50} published for a crab is 160 mg/l. Those tests that may qualify as subacute or possibly long-term show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria. No toxicity to activated sludge micro-organisms

respectively inhibition of substrate biodegradation was reported in various biodegradability tests.

Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

5.2 Recommendation

The chemical is currently of low priority for further work.

I U C L I D Data Set

Existing Chemical	Substance ID: 77-92-9
CAS No.	77-92-9
EINECS Name	1,2,3-Propanetricarboxylic acid, 2-hydroxy-
EINECS No.	201-069-1
Molecular Weight	192.12
Molecular Formula	C6 H8 O7
Producer Related Part	
Company:	F.Hoffmann-La Roche AG
Creation date:	22-MAY-00
Substance Related Part	
Company:	F.Hoffmann-La Roche AG
Creation date:	22-MAY-00
Printing date:	18-OCT-01
Revision date:	
Date of last Update:	**24-SEP-01**
Number of Pages:	**63**
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

1.0.1 OECD and Company Information

Type: sponsor country
Name: Switzerland

07-MAY-01

Type: lead organisation
Name: Swiss Agency for Environment, Forests and Landscape
Partner: Dr Urs Stämpfli **Date:**
Town: 3003 Bern
Country: Switzerland

08-MAY-01

Type: other: Sponsor Company
Name: F.Hoffmann-La Roche Ltd
Partner: Pascal Iltis **Date:**
Street: Grenzacherstrasse
Town: 4070 Basel
Country: Switzerland
Phone: 061-688'11'11
Telefax: 061-691'93'91
Telex: 962'292

08-MAY-01

Type: other: co-sponsors

Remark: ADM (Republic of Ireland), Jungbunzlauer (Switzerland), Gadot(Israel)
03-NOV-00

1.0.2 Location of Production Site

Name of Plant: European Citric Acid Manufacturers (ECAMA) Companies

Country: Belgium, Republic of Ireland, United Kingdom, Austria, Israel
Remark: Companies: Roche, ADM, T&L/Stately, Jungbunzlauer, Gadot
17-OCT-00

1.0.3 Identity of Recipients

1.1 General Substance Information

Substance type: natural substance
Physical status:
Purity: > 99 % w/w
06-DEC-00 (112)

Substance type: organic
Physical status:
Purity: > 99 % w/w
07-DEC-00 (29)

1.1.1 Spectra

1.2 Synonyms

2-Hydroxypropanetricarboxylic acid
06-DEC-00 (35)

beta-Hydroxytricarballylic acid
06-DEC-00 (22)

1.3 Impurities

CAS-No: 7732-18-5
EINECS-No: 231-791-2
EINECS-Name: water
Contents: < 1 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: sulfate
Contents: < .15 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: oxalates
Contents: < .035 % w/w
07-DEC-00 (29) (30)

CAS-No: 7440-70-2
EINECS-No: 231-179-5
EINECS-Name: calcium
Contents: < .02 % w/w
07-DEC-00 (29) (30)

CAS-No: 7439-89-6
EINECS-No: 231-096-4
EINECS-Name: iron
Contents: < .005 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: chloride
Contents: < .005 % w/w
07-DEC-00 (29) (30)

1.4 Additives

CAS-No:
EINECS-No:
EINECS-Name:

Remark: No additives are being used
06-DEC-00 (30)

1.5 Quantity

Production during the last 12 months: yes
Quantity produced :100 000 - 500 000 tonnes in 2000
Country: European Union, Eastern Europe and Israel
25-JUL-00

Production during the last 12 months: yes
Quantity produced :500 000 - 1 000 000 tonnes in 2000
Country: Worldwide
Remark: industry estimate
20-SEP-00

1.6.1 Labelling

Labelling:
Symbols: Xi
R-Phrases: (36) Irritating to eyes
S-Phrases: (24/25) Avoid contact with skin and eyes
06-DEC-00 (35)

1.6.2 Classification

Classification: as in Directive 67/548/EEC
Class of danger: irritating
R-Phrases: (36) Irritating to eyes
06-DEC-00 (35)

1.7 Use Pattern

Type: industrial
Category: other: wide dispersive use
04-SEP-00

Type: industrial
Category: other: soft drinks and beverage industry, approx. 50%
04-SEP-00

Type: industrial
Category: other: food industry, approx. 20%
04-SEP-00

Type: industrial
Category: other: pharmaceutical industry, approx. 10%
04-SEP-00

Type: industrial
Category: other: various industries (softening agent, cleaning agent,corrosive agent, synergist in antioxidant mixtures)

06-DEC-00 (25) (96)

Type: industrial
Category: other: detergent industry (complex forming agent in washing powders and detergents)
04-SEP-00

1.7.1 Technology Production/Use

Remark: Uses in Consumer Products: Processed food and beverages (solid/liquid); Pharmaceutical preparations, mainly effervescent tablets (solid); Household cleaners (liquid)
22-MAY-00

1.8 Occupational Exposure Limit Values

Type of limit: MAC (NL)
Limit value:
Remark: no data available
06-DEC-00 (48)

Type of limit: MAK (DE)
Limit value:
Remark: no data available
06-DEC-00 (48)

Type of limit: MEL (UK)
Limit value:
Remark: no data available
06-DEC-00 (48)

1.9 Source of Exposure

Memo: Exposure to concentrated solid substance or solutions is most likely during manufacturing, packaging and industrial use.
04-SEP-00

1.10.1 Recommendations/Precautionary Measures

Type: Handling

Remark: For industrial handling use eye protection with tightly fitting goggles, skin protection with acid-proof gloves and full protective working clothes.
03-NOV-00

1.10.2 Emergency Measures

Remark: In case of eye contact, rinse eyes for at least 10 minutes keeping eyelids forcibly open. For skin contact, take off affected clothing and wash skin with water and soap

only. In case of accidental ingestion drink a lot of water. If itching, soreness or irritation develops consult a doctor.

04-SEP-00

1.11 Packaging

Memo: Polyethylene-lined approved strong paper bags or fibre Drum for dry substance; food-approved plastic or stainless steel drums or tanks for aqueous solutions.

20-SEP-00

1.12 Possib. of Rendering Subst. Harmless

Type of destruction: Incineration

04-SEP-00

1.13 Statements Concerning Waste

Memo: Incinerate solids. Biological wastewater treatment for solutions.

04-SEP-00

1.14.1 Water Pollution

1.14.2 Major Accident Hazards

1.14.3 Air Pollution

1.15 Additional Remarks

Memo: The substance can be incinerated in an appropriate installation with flue gas scrubbing

05-DEC-00 (35)

1.16 Last Literature Search

Date of Search: 20-SEP-00

03-NOV-00

1.17 Reviews

Memo: HEDSET Dataset 1993
04-SEP-00 (48)

Memo: Fed. Am. Soc. Exp. Biology (1977): evaluation of the health aspects of citric acid, sodium citrate, ammonium citrate, triethyl citrate, isopropyl citrate and stearyl citrate as food ingredients.
03-NOV-00 (36)

Memo: BIBRA Toxicity profile (1993): Citric acid and its common salts
03-NOV-00 (7)

1.18 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: 201 069 1

04-SEP-00

Additional Info: RTECS accession no. GE 7350000

21-SEP-00

2.1 Melting Point

Value: = 152 - 159 degree C
Reliability: (4) not assignable
08-MAY-01 (85)

Value: ca. 153 degree C
Decomposition: no
Sublimation: no
Reliability: (4) not assignable
08-MAY-01 (19)

2.2 Boiling Point

Value:
Decomposition: yes
Remark: No boiling point due to substance decomposition above 175 degree C
Reliability: (4) not assignable
08-MAY-01 (96)

Value:
Decomposition: yes
Remark: No boiling point due to substance decomposition
Reliability: (4) not assignable
08-MAY-01 (19)

2.3 Density

Type: relative density
Value: = 1.665 at 20 degree C
Reliability: (4) not assignable
08-MAY-01 (19)

Type: bulk density
Value: ca. 500 - 950 kg/m3 at 20 degree C
Method: other: DIN 53912
Reliability: (2) valid with restrictions
21-SEP-00 (48)

2.3.1 Granulometry

2.4 Vapour Pressure

Value:
Remark: No studies located
24-SEP-01

Value:
Method: QSAR estimation
Result: 7.3 x 10E-7 Pa
24-SEP-01 (94)

2.5 Partition Coefficient

log Pow: = -1.72 at 20 degree C
Method:
Year:
Reliability: (4) not assignable
08-MAY-01 (116)

2.6.1 Water Solubility

Value: ca. 592 g/l at 20 degree C
Reliability: (4) not assignable
08-MAY-01 (77)

Value: ca. 643 g/l at 30 degree C
Reliability: (4) not assignable
08-MAY-01 (77)

Value: ca. 576 g/l at 20 degree C
Reliability: (2) valid with restrictions
05-DEC-00 (48)

Value: ca. 771 g/l
Test condition: Water at room temperature
Reliability: (2) valid with restrictions
08-MAY-01 (28)

Value: = 1330 g/l
Test condition: "cold" water
Reliability: (4) not assignable
21-SEP-00 (116)

pH: = 2.2 at .1 other: N (normal)
Test substance: Citric acid monohydrate
Reliability: (4) not assignable
08-MAY-01 (85)

pH: ca. 1.8 at 5 other: w% and 25 degree C
Test substance: Citric acid
Reliability: (2) valid with restrictions
21-SEP-00 (48)

pKa: 3.13 at 25 degree C
Remark: pKa(1)
Reliability: (4) not assignable
08-MAY-01 (77)
pKa: 4.76 at 25 degree C
Remark: pKa(2)
Reliability: (4) not assignable
08-MAY-01 (77)

pKa: 6.4 at 25 degree C
Remark: pKa(3)
Reliability: (4) not assignable
08-MAY-01 (77)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

Value: = 1010 degree C
Test substance: Citric acid powder
Reliability: (4) not assignable
08-MAY-01 (113)

2.9 Flammability

Result: non flammable
GLP: no
Remark: "Fire potential slight when heated"
Reliability: (4) not assignable
08-MAY-01 (99)

2.10 Explosive Properties

Result: other: dust explosion
Method: other: Modified Hartmann Tube
GLP: no
Remark: Dust explosible at a concentration of 500 mg/l air, substance swirled up using a defined jet of pressurised air, ignition source electrical spark. In same test series dust ignition (but not explosion, based on the energy liberated) was found starting at concentrations of 200 mg/l air.
Reliability: (1) valid without restriction
06-DEC-00 (98)

Result: not explosive
Remark: Minimum ignition energy of citric acid (particle size range 3 to 150 mcm) was between 1300 mJ (no ignition) and 4000 mJ (ignition)
Reliability: (2) valid with restrictions
06-DEC-00 (48)

2.11 Oxidizing Properties

Result: no oxidizing properties
Remark: No studies located, but not expected from structure to have oxidizing properties
08-MAY-01

2.12 Additional Remarks

Memo: Henry's Law Constant: KH<=2.3*10E-7 Pa*m3/mol
Method: QSAR estimation assuming a water solubility of >= 600 mg/l
08-MAY-01 (95)

Memo: Viscosity = 6.5 cP (50% aqueous solution) at 25 degree C
Reliability: (4) not assignable
08-MAY-01 (20)

3.1.1 Photodegradation

Type:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
25-MAY-00

3.1.2 Stability in Water

Type: abiotic
t1/2 pH 1 **:** = 72.9 year
Method: other: chemical analysis, half-life calculated
Year: **GLP:** no
Test substance:
Remark: abiotic degradation due to the reaction with OH radicals, based on literature value for OH radical concentration in water of 1*10E-17 mol/l
Result: degradation rate constant: 0.30*10E8 l/mol*s
Test condition: room temperature
Test substance: aqueous solution
Reliability: (4) not assignable
21-MAY-01 (4)

3.1.3 Stability in Soil

Type: other: biotic degradation in soil Radiolabel: no data
Concentration:
Cation exch. capac. other: not stated
Microbial biomass: other: not stated
Method: other: not stated
Year: 1977 **GLP:** no
Test substance: other TS: "citrate"
Result: "Substantial disappearance of citrate from soil is reported to occur in seven days"
Reliability: (4) not assignable
08-MAY-01 (80)

3.2 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: surface water
Result: 0.025-0.145 mg/l, Atlantic coast seawater
Reliability: (4) not assignable
24-SEP-01 (89)

Type of measurement:
Medium: surface water
Result: < 0.04-0.2 mg/l, river water
Reliability: (4) not assignable

24-SEP-01 (1) (23)

Type of measurement:
Medium: other: raw sewage
Result: Raw sewage contains up to 10 mg/l of citrate
Reliability: (4) not assignable
24-SEP-01 (80)

3.3.1 Transport between Environmental Compartments

Type:
Media:
Method:
Year:
Remark: No studies located
25-MAY-00

3.3.2 Distribution

Media: other: air-sediment-soil-water
Method:
Year:
Method: Level III, Fugacity-based Environmental Equilibrum Partitioning Model v.2.20
Remark: System default values for the environmental parameters were not changed. Water solubility 576,000 mg/l, vapour pressure 1Pa and logPow -1.72 were used for the calculation; 33% emission each to air, soil and water.
Result: 55.76% to water, 44.20% to soil, 0.02% to sediment and 0.02% to air
21-MAY-01 (72)

Media: other: air-sediment-soil-water
Method:
Year:
Method: Level I, EQC Model v.1.0
Remark: System default values for the environmental parameters were not changed. Water solubility 576,000 mg/l, vapour pressure 1 Pa and logPow -1.72 were used for the calculation.
Result: 99.99% to water, <0.01% to soil, <0.01% to sediment and <0.01% to air
21-MAY-01 (72)

3.4 Mode of Degradation in Actual Use

Result: Citric acid is found in all eukaryote cells, forming an intermediate in the Krebs cycle. It is synthesised but subsequently broken down in the course of this very basic biochemical cycle.
Citric acid is easily biodegradable by sewage treatment bacteria. It is expected to be biodegradable by common soil and sediment bacteria.
Citric acid is easily oxidised by a variety of oxidising

agents, eg, peroxides or hypochlorites. The usual oxidation products are acetonedicarboxylic acid (CAS 542-05-2), oxalic acid (CAS 6153-56-6), carbon dioxide (CAS 124-38-9) and water (CAS 7732-18-5)

24-SEP-01 (17) (48) (116)

3.5 Biodegradation

Type: aerobic
Inoculum: other: non-adapted
Result: readily biodegradable
Method: Directive 84/449/EEC, C.5 "Biotic degradation - modified Sturm test"
Year: **GLP:** no
Test substance: other TS: Not stated
Remark: Medium: sewage treatment
Result: Readily biodegradable.
97% (duration not stated), based on CO2 evolution
100% (duration not stated), based on DOC removal
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Type: aerobic
Inoculum: activated sludge, non-adapted
Degradation: = 85 % after 1 day
Kinetic: 1 day = 85 %
Method: Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn-Wellens test"
Year: **GLP:** no
Test substance: other TS: Not stated
Remark: Medium: sewage treatment
Result: inherently biodegradable, related to DOC (Dissolved Organic
Carbon)
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Type: aerobic
Inoculum: activated sludge, non-adapted
Degradation: = 98 % after 7 day
Kinetic: 7 day = 98 %
Method: Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn-Wellens test"
Year: **GLP:** no
Test substance: other TS: purity > 99%
Remark: Medium: sewage treatment
Result: inherently biodegradable, related to DOC (Dissolved Organic
Carbon)
Reliability: (2) valid with restrictions
08-MAY-01 (28)

3.6 BOD5, COD or BOD5/COD Ratio

B O D 5

Method: Directive 84/449/EEC, C.8 "Biodegradation: Biochemical Oxygen Demand"
BOD5: = 526 mgO2/l

C O D

COD: = 728 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = .72

Reliability: (2) valid with restrictions
21-SEP-00 (48)

Method: other: Coupled Units Test

Result: 93% of COD removed
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Method: Closed Bottle Test
Result: Ratio BOD30/COD = 90% of COD
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Remark: Data collated from three publications
Result: Ratio BOD5/ThOD = 58% to 61%
Reliability: (4) not assignable
08-MAY-01 (116)

Remark: Sewage treatment, initial concentration 720 mg/l, BOD determination
Result: Activated sludge after 20d: 98% of ThOD
Reliability: (2) valid with restrictions
06-DEC-00 (71)
Remark: Sewage treatment, BOD determination
Result: Activated sludge after 24h: 13% of ThOD
Reliability: (2) valid with restrictions
06-DEC-00 (74)

3.7 Bioaccumulation

Species: other: Fish
Exposure period:
Concentration:
BCF: = .01
Elimination: no
Method: other
Year: **GLP:** no
Test substance:
Remark: Estimate: logBCF (wet wt, fish)=0.85*logPow - 0.70

[for logPow < 6.0] = -2.16
Type of test: calculated
Reliability: (2) valid with restrictions
07-DEC-00 (115)

3.8 Additional Remarks

Memo: Indirect photolysis
Remark: Estimation of the indirect photolysis using a photochemical hydroxyl radical reaction constant of 7.02*10E-12 cm3/mol.sec and assuming a hydroxyl radical concentration 0.5*10E6 OH/cm3 would result in an atmospheric half life of 2.3 days (Meylan and Howard, Epiwin, SRC).
08-MAY-01 (79)

Memo: Other Information
Remark: Initial concentrations 6.5*10E-7 M citric acid, 0.01 M FeCl3
Result: In a parallel citric acid recovery tests by iron coprecipitation, only half to one third of citric acid recovered from distilled water was recovered from Lake Mendota water at pH values above 8.5, showing appreciable abiotic or biotic degradation under natural conditions
Reliability: (2) valid with restrictions
21-MAY-01 (109)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 440 - 760
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: "Solution was not neutralised"
Reliability: (2) valid with restrictions
05-DEC-00 (58)

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 1516
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
05-DEC-00 (104)

Type: other: not stated
Species: Carassius auratus (Fish, fresh water)
Exposure period:
Unit: mg/l **Analytical monitoring:**
LC0: = 625
LC100: = 894
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Exposure period: "Long-time exposure in hard water". "Hard water" buffers the acidity respectively the acid effect.
Reliability: (2) valid with restrictions
21-MAY-01 (27)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period:
Unit: mg/l **Analytical monitoring:**
EC0: = 80
EC100: = 120
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Exposure period: "Long-time exposure in soft water". "Soft water", does not buffer the acidity respectively the acid effect.
Reliability: (2) valid with restrictions

08-MAY-01 (1)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 1206
EC50: = 1535
EC100: = 2083
Method: other: not stated
Year: 1982 **GLP:** no data
Test substance:
Test condition: neutralised
Reliability: (4) not assignable
21-MAY-01 (13)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 73
EC50: = 85
EC100: = 98
Method: other: not stated
Year: 1982 **GLP:** no data
Test substance:
Test condition: not neutralised
Reliability: (4) not assignable
21-MAY-01 (13)

Species: other aquatic crustacea: Carcinus maenas (crab)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 160
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (93)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus quadricauda (Algae)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
EC0: = 640
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Species: other algae: Pavlova lutheri (saltwater chrysophytes)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC: = 1 - 300

Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

Species: other algae: Chaetoceros gracilis, Navicula ramosissima (saltwater diatoms)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC : = 1 - 300
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Microcystis aeruginosa (Bacteria)
Exposure period: 8 day
Unit: mg/l **Analytical monitoring:**
EC0: = 80
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
08-MAY-01 (10)

Type: aquatic
Species: Nitrosomonas sp. (Bacteria)
Exposure period:
Unit: mg/l **Analytical monitoring:**
NOEC : = 100
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: No inhibition on NH3 oxidation
Reliability: (2) valid with restrictions
08-MAY-01 (49)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: > 10000
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Type: aquatic
Species: other bacteria: 37 strains of bacteria

Exposure period: 30 day
Unit: mg/l **Analytical monitoring:**
EC0: = 500
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Concentration: 500 mg/l, pH=3.0; Microbes from acidic mine water (Central Pennsylvania), isolated from enrichment cultures, test substance as C source in static culture
Result: positive growth on all strains
Reliability: (2) valid with restrictions
08-MAY-01 (121)

Type: other: not stated
Species: Entosiphon sulcatum (Protozoa)
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 485
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Type: other: not stated
Species: other bacteria: Arthrobacter globiformis, 10 strains
Exposure period: 5 day
Unit: **Analytical monitoring:**
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Microbes isolated from soil, test substance as sole C source, mineral salts added
Result: good to excellent degradation with all strains
Reliability: (2) valid with restrictions
21-MAY-01 (56)

Type: other: not stated
Species: other protozoa: Tetraselmis tetrathele (saltwater)
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC : = 1 - 300
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

Type: other: not stated
Species: other protozoa: Tetramitus rostratus (freshwater)
Exposure period: 35 hour(s)
Unit: mg/l **Analytical monitoring:**
TLC : <= 108
Method: other: not stated
Year: **GLP:** no data
Test substance:

Reliability: (4) not assignable
24-SEP-01 (55)

Type: other: not stated
Species: Uronema parduzci (Protozoa)
Exposure period:
Unit: mg/l **Analytical monitoring:**
TLC : = 622
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
21-MAY-01 (11)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: No studies located, with the possible exception of the one recorded under 4.1
14-JUL-00

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: No studies located with the possible exception of the one recorded chapter 4.2
21-SEP-00

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type:
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
14-JUL-00

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: All plants produce citric acid as an intermediate of the Krebs cycle.
No studies located.
08-MAY-01 (24) (96)

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
03-NOV-00

4.7 Biological Effects Monitoring

Remark: Based on the low n-octanol/water partition coefficient on one hand and based on the fact that citric acid as an intermediate in the Krebs cycle (see 4.8) is transformed into other substances in every body cell of eukaryotes on a daily basis, no biomagnification is given.
No studies located.
05-DEC-00

4.8 Biotransformation and Kinetics

Type:
Result: Citric acid is an intermediate in the citric acid or Krebs cycle, also known as the tricarboxylic acid cycle, which takes place in every eukaryote cell and which breaks down glucose through glycolysis
08-MAY-01 (17)

4.9 Additional Remarks

Memo: (a)
Result: Citric acid is "extremely widesprad in nature"
21-MAY-01 (37)

Memo: (b)
Result: Citric acid is "widely distributed in plants and animal tissues and fluids"
08-MAY-01 (77)

Memo: (c)
Result: In man, during 24h approxymately 2000 g of citric acid are formed and further metabolised as intermediates in the citric acid cycle in adults
08-MAY-01 (96)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: mouse
Sex: male/female
Number of Animals: 10
Vehicle:
Value: = 5400 mg/kg bw
Method:
Year: 1981 **GLP:** no
Test substance:
Remark: 5 male and 5 female mice in each treatment group were administered 3000 mg/kg, 4243 mg/kg, 6000 mg/kg, 8485 mg/kg or 12000 mg/kg of citric acid by gavage. The test substance was dissolved in pure water at such concentrations that in every group 20 ml/kg were given. Controls were administered 0.4 ml tap water by gavage.
Reliability: (2) valid with restrictions
08-MAY-01 (32)

Type: other: lethal dose
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 7000 mg/kg bw
Method:
Year: **GLP:** no
Test substance:
Remark: Probably lowest Lethal dose
Reliability: (4) not assignable
21-MAY-01 (119)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3000 mg/kg bw
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
06-DEC-00 (88)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 12000 mg/kg bw

Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 5000 mg/kg bw
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

5.1.2 Acute Inhalation Toxicity

Type:
Species:
Sex:
Number of Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
17-JUL-00

5.1.3 Acute Dermal Toxicity

Type:
Species:
Sex:
Number of Animals:
Vehicle:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
17-JUL-00

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:

Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: = 5500 mg/kg bw
Method: Other
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: = 2700 mg/kg bw
Method: Other
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: An irritant skin dermatitis attributed to citric acid has been reported amongst waiters and bakers.
16-MAY-01 (38)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:

Method:
Year: **GLP:**
Test substance:
Remark: In solution, the acid may produce pain if applied to abraded skin.
08-MAY-01 (46)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: A 0.3 N solution (approximatively 2%) can "sting" intact skin, this appears unrelated to irritant potential.
08-MAY-01 (65)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Patch testing of 60 eczema patients with 2.5 % citric acid in petrolatum (probably 24 h covered contact) did not produce any irritant reactions.
Reliability: (4) not assignable
08-MAY-01 (83)

Species: other: rabbit, New Zealand White, > 3 kg bw
Concentration: other: 30% aqueous solution

Exposure: Occlusive
Exposure Time:
Number of Animals: 3
PDII:
Result: not irritating
EC classificat.: not irritating
Method: Draize Test
Year: **GLP:** no
Test substance:

Remark: Dose=0.5ml (corresponding to 0.15 g in aqueous solution) during 4 h under occlusive patch; subsequent observations at 4 h, 24 h and 48 h. Effects reported as nil (no erythema/eschar, no oedema) for intact skin, effects reported as "slight to well defined" in one instance for abraded skin. Overall Primary Irritation Index (average of all observations) = 0.84, hence in this test the substance is not a primary skiirritant.
Reliability: (1) valid without restriction
08-MAY-01 (33)

Species: rabbit
Concentration:

Exposure:
Exposure Time: 24 hour(s)
Number of Animals:
PDII:
Result: slightly irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: Dose=500 mg/24 h; Effects reported as "mild"
Reliability: (4) not assignable
21-MAY-01 (75)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: slightly irritating
EC classificat.: not irritating
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: **GLP:** no data
Test substance:
Remark: "Average result of 24, 48 and 72 hours: erythema score=0.33, oedema score=0"
Reliability: (4) not assignable
21-MAY-01 (63)

5.2.2 Eye Irritation

Species: other: rabbit, New Zealand White, > 2 kg bw
Concentration: other: 10% and 30% aqueous solution
Dose:
Exposure Time:
Comment:
Number of Animals: 3
Result: not irritating

EC classificat.: not irritating
Method: Draize Test
Year: **GLP:** no
Test substance:
Remark: Dose=0.1 ml (corresponding to 0.01 g resp. 0.03 g in aqueous solution) is placed into the lower conjunctival sac of one eye held closed for one second; subsequent observation period was14 days. Effects of the 10% solution reported as moderate to weak conjunctival irritation disappearing within one week, without further effects on the cornea. Overall Primary Eye Irritation Index (Draize score, average of all observations) = 9.3 for the 10% solution, resulting in a classification of "minimally irritating". Effects of the 30% solution reported as well-defined to moderate conjunctival irritation which disappeard in two of the three rabbits within 14 days; additionally, a short-lasting superficial lesion of the conjunctival epithelium was noted; no macroscopical alteration of the cornea was observed. Overall Primary Eye Irritation Index (Draize score, average of all observations)=16.0 for the 30% solution, resulting in a classification of "mildly to moderately irritating"
Reliability: (1) valid without restriction
07-DEC-00 (34)

Species: human
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Severe damage was reported in a patient who was splashed in the eye with a saturated solution of citric acid.
Reliability: (4) not assignable
21-MAY-01 (118)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance: other TS: 0.5% aq. solution, 2% solution aq.
Remark: "Irrigation for 30 min with 0.5% to 2% solution causes severe injury; the 0.5% solution causes permanent

cloudiness of the cornea and the 2% solution causes severe dense opacification"
Reliability: (4) not assignable
16-MAY-01 (43)

Species: rabbit
Concentration:
Dose: 750 other: ug/24 h
Exposure Time:
Comment:
Number of Animals:
Result: highly irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: Effect reported as "severe"
Reliability: (4) not assignable
16-MAY-01 (75)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: highly irritating
EC classificat.: irritating
Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: **GLP:** no data
Test substance:
Remark: "Average results of 24, 48 and 72 hours: cornea score = 2.8, iris score = 0.0, conjunctiva score = 1.7"
Reliability: (4) not assignable
16-MAY-01 (63)

5.3 Sensitization

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: Mouth sores (canker sores), headache, asthma, nasal blockage, general tiredness and itchiness were some of the symptoms reported by a man after the ingestion of foods containing citric acid. Application of crystals to the inside surface of the mouth produced sores (as did some other organic acids) but potassium citrate crystals

and magnesium citrate solution did not. Control subjects did not react to mouth application of citric acid.

16-MAY-01 (111)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: A standard text implies that citric acid might be a skin sensitizer by recommending 1% aqueous solutions for (24/48-hr covered) patch-tests to detect the sensitized state.

16-MAY-01 (38)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: No allergic reactions were seen when 60 patients with hand eczema, all of whom were involved in handling food, were patch tested (covered contact, probably 24 hr) with 2.5% citric acid in petrolatum.

16-MAY-01 (83)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: Urticaria (a skin complaint) and mouth ulcers have been noted following exposure to citric acid [no other details were given].

21-MAY-01 (110)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain:

Route of admin.: other: oral, gavage
Exposure period: 5 days
Frequency of treatment: Once daily
Post. obs. period: 10 days
Doses: 2000 mg/kg/day, 4000 mg/kg/day, 8000 mg/kg/day, 16000 mg/kg/day
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: 10 males and 10 females, avg weight = 150 g
Result: NOEL = 4000 mg/kg
LD50 = 5600 +- 440 mg/kg/d, identical for males and females
Reliability: (1) valid without restriction
16-MAY-01 (31)

Species: mouse **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Decreased growth and lower survival times (11-13 months as opposed to 16-17 months in the untreated controls) were reported in male mice receiving 5% citric acid in the diet (about 7.5 g/kg bw/day) for an unspecified period.
Reliability: (4) not assignable
16-MAY-01 (124)

Species: rabbit **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No adverse effects were seen in limited studies in 15 rabbits receiving 7.7% sodium citrate (equivalent to 5% free citric acid) in the diet (about 1.5 g citric acid/kg bw/day) for 150 days.

Result: NOAEL = 1500 mg/kg/d
Reliability: (4) not assignable
16-MAY-01 (90)

Species: dog **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No adverse effects were seen in three dogs fed daily doses of 1.38 g citric acid/kg bw for up to 120 days.
Result: NOAEL = 1400 mg/kg/d
Reliability: (4) not assignable
21-MAY-01 (64)

Species: guinea pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: A reduced packed cell volume in the blood was the only effect noted in guinea-pigs receiving diets supplements with 1-5% citric acid (about 0.4-2 g/kg bw/day) for a maximum of 60 days. No tissue examinations were undertaken. (The unsupplemented diets contained around 1.2% citric acid, so actual citric acid intakes were greater than the quoted values).
Reliability: (4) not assignable
16-MAY-01 (123)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:

Year: **GLP:** no data
Test substance:
Remark: Body weight gain was unaffected in young pigs fed a cadmium-enriched diet containing 5% citric acid (corresponding to about 4 kg/kg bw/day). Cadmium levels were, however, elevated in the liver and kidneys and the zinc level was decreased in muscle in citric acid/cadmium treated pigs compared with pigs treated with cadmium only.
Reliability: (4) not assignable
21-MAY-01 (100)

Species: sheep **Sex:**
Strain:
Route of admin.: other: ruminal cannula
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: When six sheep were given 795 mg citric acid/kg bw/day for 60 days via a ruminal cannula, no effects were seen on feed intake, weight gain or mineral metabolism.
Reliability: (4) not assignable
16-MAY-01 (3)

Species: rat **Sex:** male/female
Strain:
Route of admin.: other: oral, dietary
Exposure period: 90 weeks
Frequency of treatment: Daily (feed)
Post. obs. period: Not stated
Doses: Feed containing 1.2% citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Cited as "... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed. Although a slight increase in dental attrition was reported."
Reliability: (2) valid with restrictions
21-MAY-01 (8)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral, dietary
Exposure period: 6 weeks
Frequency of

treatment:
Post. obs. period:
Doses: Feed containing 1.2, 2.4, 4.8% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: Japanese investigators have recorded slight growth reduction in groups of 10 male rats fed 1.2, 2.4 or 4.8% citric acid (apparently 1.15, 2.26 or 4.67 g/kg bw/d) for 6 weeks and, at the top dose, mild blood and urine changes and slight degeneration of the thymus gland and the spleen.
Reliability: (4) not assignable
21-MAY-01 (125)

Species: rat **Sex:**
Strain:
Route of admin.: other: oral dietary
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 2% citric acid
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Citric acid had no effects on food consumption or body weight when fed at a dietary level of 2% (about 0.13 g/kg bw/d) to nine rats. The absorption and urinary excretion of calcium and magnesium were unaffected, although urinary zinc excretion was temporarily elevated.
Reliability: (4) not assignable
21-MAY-01 (103)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral dietary
Exposure period: 2 years
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 5% and 3% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: In 2 year studies with groups of 20 male rats, dietary levels of 5% citric acid (about 2g/kg bw/d) or 3% slightly decreased growth (food consumption was also lower in the top-dose group), but no tissue

abnormalities were found on examination of the major organs.
Result: NOAEL = 1200 mg/kg/d
Reliability: (4) not assignable
21-MAY-01 (50)

Species: rat **Sex:**
Strain:
Route of admin.: other: oral dietary
Exposure period: 1 year
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 1.2% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No adverse effects were reported (with the possible exception of slight changes in tooth structure) when two successive generations of rats were fed 1.2% citric acid (about 600 mg/kg bw/d) and 0.1% sodium citrate in the diet for apparently up to about 1 year (only a limited range of tissues was examined microspically).
Reliability: (4) not assignable
21-MAY-01 (8)

5.5 Genetic Toxicity 'in Vitro'

Type: Bacterial reverse mutation assay
System of testing: Species/strain: Salmonella typhimurium TA 97, TA 98, TA 100, TA 104
Concentration: Not stated
Metabolic activation: with and without
Result: negative
Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: **GLP:** no data
Test substance:
Remark: Activation system: Liver homogenate from rats pretreated with phenobarbital
Reliability: (2) valid with restrictions
16-MAY-01 (2)

Type: Bacterial reverse mutation assay
System of testing: Species/strain: Salmonella typhimurium TA 94, TA 98, TA 100, TA 1535, TA 1537
Concentration: Up to 5 mg/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: **GLP:** no data
Test substance:
Remark: Activation system: Liver homogenate from rats preteated with polychlorinated biphenyl KC-400
Reliability: (2) valid with restrictions
21-MAY-01 (54)

Type: Bacterial reverse mutation assay
System of testing: Escheria coli
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
16-MAY-01 (47)

Type: Yeast gene mutation assay
System of testing: Not stated
Concentration: > 3.5 g/kg
Metabolic activation: with and without
Result: negative
Method: other
Year: **GLP:** no
Test substance:
Reliability: (4) not assignable
21-MAY-01 (70)

Type: Yeast gene mutation assay
System of testing: Saccharomyces cerevisiae

Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:** no
Test substance:
Reliability: (4) not assignable
21-MAY-01 (69)

Type: other: clastogenic assay
System of testing: Fibroblast culture from chinese hamster (Cricetulus griseus)
Concentration: Up to 1mg/ml
Metabolic activation:
Result:

Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: No clastogenic effects reported
Result: Genotoxic effects: negative
Reliability: (2) valid with restrictions
21-MAY-01 (54)

5.6 Genetic Toxicity 'in Vivo'

Type: Dominant lethal assay
Species: rat **Sex:** no data
Strain:
Route of admin.: unspecified
Exposure period:
Doses:
Result:
Method:
Year: **GLP:** no
Test substance:
Remark: No mutagenic potential was detected in a dominant lethal assay in rats in which doses of up to 3 g citric acid/kg bw/day were administrated for 5 days. (A dominant lethal effect is normally reflected by increased early foetal death when treated males are mated with untreated females).
Reliability: (4) not assignable
21-MAY-01 (69)

Type:
Species: rat **Sex:** no data
Strain:
Route of admin.: unspecified
Exposure period:
Doses:

Result:
Method:
Year: **GLP:** no
Test substance:
Remark: No chromosomal damage occurred in the bone marrow of rats ingesting up to 3 g citric acid/kg bw/day for 5 days.
Reliability: (4) not assignable
21-MAY-01 (69)

5.7 Carcinogenicity

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs.

period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: In a limited study, no evidence of carcinogenicity was reported in 20 male rats receiving up to 5% citric acid in the diet (about 2g/kg bw/day) for 2 years. (Modern regulatory guidelines recommend that groups of 50 rodents of each sex are exposed to one of several doses and that a comprehensive range of tissues is examined microscopically).
Reliability: (4) not assignable
21-MAY-01 (50)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Male rats were fed citric acid or sodium citrate at dietary levels providing about 2.6 g/kg bw/day (based on their final body weights) for 20 weeks and were simultaneously given a known bladder carcinogen in their drinking water.
More carcinomas (malignant tumours) were induced in rats treated with carcinogen and sodium citrate than in those treated with carcinogen alone, however, this was attributed to the increased water intake (and hence carcinogen intake) in this group. Citric acid did not have a tumour promoting effect.
Reliability: (2) valid with restrictions
24-SEP-01 (53)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:

Year: **GLP:** no data
Test substance:
Remark: No increase in DNA synthesis (a measure of cell proliferation) in the bladder epithelium was found in rats fed 1.7% sodium citrate (about 0.74 g/kg bw/day) in the diet for 8 weeks.
Reliability: (4) not assignable
16-MAY-01 (86)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral, stomach tube
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: Three liver tumours developed in a group of 80 male rats treated with a known carcinogen and receiving 470 mg citric acid/kg bw three times daily by stomach tube for up to 45 weeks. (No control animals were apparently used in this study, but clearly citric acid did not act as a potent tumour promoter).
Reliability: (4) not assignable
21-MAY-01 (6)

Species: rat **Sex:** male
Strain: other: Albino Carworth
Route of admin.: oral feed
Exposure period: 24 months
Frequency of treatment: Daily
Post. obs. period: Not stated
Doses: 2g/kg body weight/day
Result:
Control Group: yes, concurrent no treatment
Method: other
Year: **GLP:** no
Test substance:
Result: No differences between controls and experimental group
Reliability: (2) valid with restrictions
16-MAY-01 (50)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs.

period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Tumour yield increased when groups of 20 to 25 male rats who had been treated with a known bladder carcinogen were then given 5% sodium citrate in the diet (about 2.5 g/kg bw/day) for 32 weeks, then 5% sodium citrate in the diet for 4 weeks (actual intake about 1.9 g/kg bw/day), followed by a 3-week period of treatment with uracil (to accelerate tumour promotion), and then the sodium citrate for a further 9 weeks.
The incidence of bladder papillomas (benign tumours) was increased in rats treated with sodium citrate (and carcinogen/uracil) compared with those treated with only the carcinogen uracil. One of fifteen rats in the sodium citrat-treated group developed a bladder carcinoma. No papillomas or carcinomas developed in rats treated with sodium citrate and uracil but not carcinogen.
Reliability: (4) not assignable
16-MAY-01 (117)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: When the sodium citrate level was only 1.7% (actual intake about 0.74 g/kg bw/day) no effects were seen on the bladder tumour incidence in rats treated with citrate (and carcinogen/uracil) compared with those treated with carcinogen and uracil only. However, if the 1.7% sodium citrate treatment was combined with the administration of two other sodium salts (the ascorbate and bicarbonate), the yield of papillomas and carcinomas was increased in a synergist fashion.
Reliability: (4) not assignable
16-MAY-01 (86)

5.8 Toxicity to Reproduction

Type:
Species: rat **Sex:**
Strain:

Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No effects on reproduction were reported in limited studies in which rats were fed diets containing 1.2% citric acid (about 600 mg/kg bw/day) and 0.1% sodium citrate for 29 weeks prior to mating and then for another few months.
Reliability: (4) not assignable
21-MAY-01 (8)

Type:
Species: rat **Sex:**
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity (malformations in the offspring) or other adverse effects when female rats received up to 295 mg citric acid/kg bw/day on days 6 to 15 of pregnancy.
Reliability: (4) not assignable
21-MAY-01
(39)

Type:
Species: rat **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No teratogenicity or other adverse effects were reported when females received up to 241 mg citric acid/kg bw on days 6 to 15 of pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type:
Species: mouse **Sex:** female
Strain:
Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Litter size and survival of offspring up to weaning were unaffected when female mice consumed 5% citric acid in the diet (about 7.5 g/kg bw/day) previous to, during, and subsequent to mating.
Result: NOEL = 7500 mg/kg/d
Reliability: (4) not assignable
16-MAY-01
(124)

Type:
Species: rabbit **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity or other adverse effects when female rabbits were given up to 425 mg/kg bw on days 6 to 18 of pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type:
Species: hamster **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity or other adverse effects when female hamsters received up to 272 mg citric acid/kg (presumably daily) on days 6 to 10 of

pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type: Two generation study
Species: rat **Sex:** male/female
Strain:
Route of admin.: other: oral, dietary
Exposure Period: 90 weeks
Frequency of treatment: Daily (feed)
Duration of test:
Doses: Feed containing 1.2 w/w % citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Cited as "... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed, although a slight increase in dental attrition was reported."
Reliability: (2) valid with restrictions
07-DEC-00 (8)

Type:
Species: rat **Sex:** female
Strain:
Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No effects on reproduction were reported in a study in which female rats ingested 5% citric acid (about 2.5 g/kg bw/day) previous to, during and subsequent to mating.
Result: NOEL = 2500 mg/kg/d
Reliability: (4) not assignable
21-MAY-01
(124)

5.9 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain:
Route of admin.: other: not stated
Exposure period: Not stated
Frequency of treatment: Daily
Duration of test: Days 6 to 15 of gestation

Doses: > 241 mg/kg body weights per day
Control Group: no data specified
Method: other
Year: **GLP:** no data
Test substance:
Result: "No indication of adverse effects on nidation, maternal or foetal survival. The number of abnormalities did not differ from control group."
Reliability: (4) not assignable
16-MAY-01 (39)

Species: other: rats and mice **Sex:** male/female
Strain:
Route of admin.: other: oral, diet
Exposure period: Not stated
Frequency of treatment: Not stated
Duration of test: Not stated
Doses: Feed containing 5% citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: "5% Citric acid did not depress food intake but caused a loss in body weight gain and reduced survival time in mice, with a slightly greater influence on mature animals." ... "No effect was detected on the litter size or survival up to weaning of young in mice or rats."
Reliability: (4) not assignable
16-MAY-01 (124)

5.10 Other Relevant Information

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: Citric acid and its salts injected by various routes into rats, mice and rabbits caused nervous system, lung, spleen and liver effects, some of which were attributed to physiological disturbances (acidosis and calcium deficiency).
Reliability: (4) not assignable
21-MAY-01 (44) (50) (125)

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: Intravenous infusion of rats with sodium citrate solution (25 mM) was shown to increase calcium excretion.
Reliability: (4) not assignable
21-MAY-01 (9)

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: No significant cardiovascular effects or effects on blood composition were seen in six horses injected intravenously with 0.56 mg sodium citrate/kg bw.

Reliability: (4) not assignable
21-MAY-01 (51)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: The effects of citric acid in mice and rats include physiological disturbances (acidosis and calcium deficiency).
16-MAY-01 (36)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: Severe damage to the stomach lining and nervous system effects were reported in rats, mice and rabbits receiving high doses of citric acid.
Reliability: (4) not assignable
21-MAY-01 (119) (125)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: The administration of 2ml/kg of a 500 mN citric acid solution (64 mg/kg bw) to rats by stomach tube decreased the volume of gastric juice secreted and the pepsin activity, but increased the total gastric acid content of the stomach.
Reliability: (4) not assignable
16-MAY-01 (81)

Type: other: Toxicity consideration
Remark: Citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological availabilty of iron and calcium.
16-MAY-01 (97) (124)

Type: other: Toxicity consideration
Remark: Other studies suggest that dietary citric acid and its salts may enhance calcium absorption and excretion and the absorption of sodium.
21-MAY-01 (18) (21) (92) (102)

Type: other: Toxicity consideration
Remark: It has been shown in an in vitro system for the development of artificial caries, that the application of citric acid to teeth may make them more susceptible to decay.
16-MAY-01 (73)

Type: other: Toxicity consideration
Remark: No formal acceptable daily intake level has been specified by the joint FAO/WHO Expert Committee on Food Additives since it was felt that citric acid and its calcium, potassium and sodium salts did not constitute a significant toxicological hazard to man when used according to good manufacturing practice.
A similar view was expressed by the EC's Scientific Committee for Food when it evaluated citrate.
16-MAY-01 (105) (120)

Type: other: Toxicity consideration
Remark: Citric acid and its salts may increase the absorption and retention of ingested metals such as aluminium, tin, cadmium and lead.
21-MAY-01 (42) (57) (60) (62) (100) (107) (108) (114)

Type: other: Toxicity consideration
Remark: Bovine teeth immersed in a soft drink containing 2.6 g citric acid/l were eroded within 2 hours.
21-MAY-01 (78)

Type: other: Toxicity consideration
Remark: Severe ulceration and tissue damage occured in dogs receiving tongue applications of 0.1ml of 50% citric acid solution (presumably aqueous) for 5 minutes.
21-MAY-01 (67)

Type: other: Toxicity consideration
Remark: Bronchoconstriction was induced with citric acid (of unspecified concentration) in dogs, which have non-specific airway hyperactivity.
21-MAY-01 (68)

Type: other: Toxicity consideration
Remark: When 14 guinea-pigs were exposed for 30 minutes to atmospheric citric acid concentrations of 31.1 or 81 mg/m3 (obtained by aerosolizing 4 or 6% solutions respectively), only one cough was recorded at the lower concentration, but significant coughing occured in the top group.
16-MAY-01 (126)

Type: other: Toxicity consideration
Remark: Coughing was produced in guinea-pigs exposed to 75 mg citric acid/ml as an aerosol for 3 minutes. Bronchoconstriction occured after 3-4 minutes.
16-MAY-01 (40)

Type: other: Toxicity consideration
Remark: Coughing occured frequently when 1 ml of an aqueous 0.27 M (about 52 g/l; 5.2%) solution of citric acid was instilled into the lower drachea (windpipe) of lambs, an effect which was not apparently seen when the acid was instilled into the mid-drachea or laryngeal area.
21-MAY-01 (52)

Type: other: Toxicity consideration
Remark: Mouth ulcers may be provoked by citric acid (human).
21-MAY-01 (38)

Type: other: Toxicity consideration
Remark: The lowest concentration of inhaled citric acid required to produce involuntary coughing in 23 men ranged from 0.5 to 32 mg/ml.
16-MAY-01 (101)

Type: other: Toxicity consideration

Remark: Citric acid (of unspecified concentration) induced bronchoconstriction) in human asthmatics.
16-MAY-01 (68)

Type: other: Toxicodynamics, Toxicokinetics
Remark: No studies located
16-MAY-01

5.11 Experience with Human Exposure

Remark: Systemic effects, single exposure (human, oral): a young woman vomited and almost died after ingesting a single dose of 25g citric acid [about 417 mg/kg bw].
21-MAY-01 (82)

Remark: Systemic effects, single exposure (human, injection): transfusions of large volumes of citrated blood may cause depletion of body calcium (hypocalcaemia) and effects on blood composition which may be accompanied by nausea, exacerbation of muscle weakness, breathing difficulties and even cardiac arrest.
21-MAY-01 (15) (16) (59) (106) (122)

Remark: General systemic effects, repeated exposure (human): minor gastrointestinal disturbances (diarrhoea, indigestion, nausea and "burning") were experienced by 22 out of 81 patients taking potassium citrate in water and seven out of 75 taking solid potassium citrate (dose unspecified in both cases) for the treatment of kidney stones.
21-MAY-01 (91)

Remark: Literature review: excretion of citric acid in 82 male and female adults ranges from 1.5 to 3.68 mmol/d (total range 0.4-8.80 mmol/d) respectively from 290 to 707 mg/d (total range 80-1,690 mg/d).
21-MAY-01 (66)

Result: Man's total daily consumption of citric acid from natural sources and from food additive sources may exceed 500 mg/kg
17-MAY-01 (124)

Remark: Citric acid ingested frequently or in large quantities may cause tooth erosion and local irritation.
17-MAY-01 (76)

Remark: Fourteen volunteers given oral doses of up to 73.5 m Eq (24.5 mmol) citrate as potassium-magnesium citrate, tripotassium citrate or trimagnesium citrate during the course of a bioavailability study did not suffer any overt gastrointestinal side effects.
17-MAY-01 (61)

Remark: General systemic effects, repeated exposure (human): potassium and sodium citrate (as the monohydrate and

dihydrate respectively) have been used presumably without marked side effects as medications in dose of up to 15 g/day.

21-MAY-01 (76) (120)

Remark: Three patients who ingested potassium citrate solution (one took an unknown large volume, probably on more than one occasion, two ingested 200-400 ml over 5-7 days) suffered abnormal heart rhythms, probably due to excessive potassium levels rather than to the citrate ion.

21-MAY-01 (14) (26)

Remark: The acid-base balance of the blood was affected in 10 men who ingested 60 ml of a solution containing 100 mg sodium citrate/ml daily (i.e. about 0.86 mg/kg bw/d) for 4 days. Their urine became more alkaline and the amount of sodium excreted was increased while that of magnesium and potassium was decreased.

21-MAY-01 (87)

Remark: Tooth erosion through dissolution of the enamel due to the acid effect in aqueous solution has been reported

21-MAY-01 (5)

Remark: Citric acid fumes apparently affected the teeth of exposed workers.

21-MAY-01 (45)

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Robust Study Summaries

Citric Acid (CAS No. 77–92–9)

PHYSICAL/CHEMICAL ELEMENTS

1) Melting Point

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1969

Results
- Melting Point Value: 152–159 ^{o}C

Conclusions

Data Quality
- Reliabilities: not assignable

References (Free Text)
- OHS Material Safety Data Sheet (10 September 1998), MDL Information Systems, Nashville, Tennessee, USA

Other
-

2) Boiling Point

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1989

Results
- Value: –
- Decomposition: yes
- Remark: no boiling point due to substance decomposition above 175 ^{o}C

Conclusions
- The boiling point could not be determined due to substance decomposition

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Römpps Chemie-Lexikon, 9th ed. Georg Thieme, Stuttgart, 1989

Other

3) Vapour Pressure

Test Substance
- Citric Acid (CAS: 77–92–9)

Method
- Method: QSAR estimation

Results
- Value: 7.3×10^{-7} Pa at 25 °C

Conclusions

Data Quality
- –

References (Free Text)
- QSAR, Epiwin 3.05 Syracuse Research Co.

Other
- –

4) Partition Coefficient

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1983

Results
- Log Pow: –1.72
- Temperature: 20 ^{o}C

Conclusions
- –

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Verschueren: Handbook of Environmental Data of Organic Chemicals, 3rd ed. Van Nostrand Reinold, New York, 1996

Other
- –

5) Water Solubility: Solubilities and *p*Ka Values

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1989

Results
- Solubility value: 592,000 mg/l at 20 °C
- Solubility value: 643,000 mg/l at 30 °C
- pKa_1 = 3.13 at 25 °C
- pKa_2 = 4.76 at 25 °C
- pKa_3 = 6.4 at 25 °C

Conclusions
- Freely soluble in water
- Substance is partly present in ionised form at all environmentally relevant *p*H values.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- The Merck Index, 11th edition, 1989

Other
- –

5) Water Solubility: *p*H Value

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1998

Results
- *p*H value: 2.2 at 0.1 *N*

Conclusions
- –

Data Quality
- Reliabilities: not assignable

References (Free Text)
- OHS Material safety Data Sheet (10 September 1998), MDL Information Systems, Nashville, Tennessee, USA

Other
- –

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

6) Photodegradation

Test Substance
- Citric Acid (CAS: 77–92–9)

Method
- Method:
- GLP:
- Year:

Results
- No studies located

Conclusions
- –

Data Quality
- –

References (Free Text)
- –

Other
- –

7) Stability in water

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Test type: abiotic degradation, no details stated
- Method: chemical analysis, half-life calculated
- GLP: no
- Year: 1967

Results
- $t_{½}$ at *p*H 1 = 72.9 years (calculated)
- Degradation rate constant: 0.30×10^{8} l/mol·s at room temperature in aqueous solution

Conclusions
- Remarks: abiotic degradation due to the reaction with OH radicals, based on literature value for OH radical concentration in water of 1×10^{-17} mol/l

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Anbar, Neta: A compilation of specific biomolecular rate constant for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int J Appl Radiat Isotopes 18: 493–523, 1967.

Other
- –

8) Transport between Environmental Compartments (Fugacity)

Test Substance

- Citric Acid (CAS: 77–92–9)

Method

- Method: Static environmental distribution model based on physicochemical parameters: Level I, EQC Model v.1.0
- Year: 1996

Results

- Media: air, sediment, soil and water
- Values: 99.99% to water, <0.01% to soil, <0.01% to sediment and <0.01% to air
- Remarks: Default values for the environmental parameters were not changed. Water solubility 592,000 mg/l, vapour pressure arbitrarily assigned 1 Pa and logPow –1.72 were used for the calculation.

Conclusions

- Practically no partitioning to air, soil and sediment, substance distributes heavily to water.

Data Quality

- –

References (Free Text)

- Mackay D, Di Guardo A, Paterson S, Cowan CE: Evaluating the environmental fate of a variety of chemicals using the EQC model. Environ Toxicol Chem 15: 1627–1637, 1996.

Other

- EQC software is available free at http://www.trentu.ca/academic/aminss/envmodel/models.html

9) Biodegradation

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: Directive 84/449/EEC, C.5 „Biotic degradation – modified Sturm test“
- Duration: not stated, probably 28 days (regular duration of test according to guideline)
- GLP: no
- Year: 1979
- Medium: water with activated sludge

Results
- Values: 97%, based on CO_2 evolution
  100%, based on DOC removal

Conclusions
- Readily biodegradable

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox Environm Safety 3: 159–173, 1979

Other
- –

ECOTOXICITY ELEMENTS

10) Acute Toxicity to fish

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Type: static
- GLP: no
- Year: 1978
- Species: *Leuciscus idus* (golden orfe, freshwater)
- Exposure period: 96 hours

Results
- Value: LC_{50} = 440–760 mg/l
- Remarks: solution was not neutralised

Conclusions
- Low toxicity for fish

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Juhnke, Lüdemann: Z Wasser Abwasserforsch. 11: 161, 1978

Other
- –

11) Toxicity to aquatic plants

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1980
- Species: *Scenedesmus quadricauda* (Algae, freshwater)
- Exposure period: 7 days

Results
- Value: EC_0 = 640 mg/l

Conclusions
- Low toxicity for algae

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Bringmann, Kühn: Water Res 14: 231–241, 1980

Other
- –

12) Acute toxicity to aquatic invertebrates

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1969
- Species: Daphnia magna (Crustacea)
- Exposure period: “Long-time exposure period in soft water”.

Results
- Values: EC_0 = 80 mg/l
  EC_{100} = 120 mg/l

Conclusions
- Geometric mean EC_{50} = 98 mg/l
- „Soft water“ does not buffer the acidity respectively the acid effect of the test substance.
- Low toxicity for daphnids

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- A.N. Khomenco et al: Gidrokhim. Mater 50: 96–101, 1969

Other
- –

HEALTH ELEMENTS

13) Acute toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: > 99%

Method
- Type: acute oral toxicity study
- GLP: no
- Year: 1981
- Species: mouse, SPF, albino, source on record
- Sex: male + female
- Number of animals: 5 males + 5 females per treatment respectively control group, 60 animals in total in main study.
- Housing: single sex groups in macrolon cages, with ad libitum access to water and NAFAG 850 complete rodent maintenance diet feed, in a climate-controlled room with environmental parameters defined and on record
- Route of administration: oral, gavage
- Range-finding study: Performed with the following doses: 2,000 mg/kg, 2,828 mg/kg, 4,000 mg/kg, 5,657 mg/kg, 8,000 mg/kg and 10,000 mg/kg; 100% mortality after 24 h in highest dose group, 50% at 8,000 mg/kg, 20% at 5,657 mg/kg and 0% in all lower dose groups.
- Description main study: 5 male and 5 female mice in each treatment group were administered 3,000 mg/kg, 4,343 mg/kg, 6,000 mg/kg, 8,485 mg/kg or 12,000 mg/kg of citric acid by gavage. The test substance was dissolved in food grade tap water at such concentrations that in every group 20 ml/kg, corresponding to approx. 0.4 ml per animal, were given. Controls were administered 0.4 ml tap water by gavage. Clinical symptoms were observed 2 h and 24 h after administration. The survivors were followed-up for 10 days after dosing, mortalities were recorded daily, then survivors were sacrificed.
- LD_{50} was calculated using probit analysis and rounded to the nearest 100 mg value.

Results
- Value: LD_{50} = 5400 mg/kg bw, 95% confidence interval = 4,500–6,400 mg/kg.
- All mortalities occurred in the first 24 h after administration.

Conclusions
- Low toxicity to mic e.

Data Quality
- Reliabilities: reliable with restriction

References (Free Text)
- F. Hoffmann-La Roche Ltd, unpublished report, 1981

Other
- –

14) Genetic toxicity *in vivo* (chromosomal aberrations)

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Type: Dominant lethal assay
- Species: rat
- Sex: males (treated) and females (untreated)
- Number of animals: not stated
- Route of administration: oral
- Year: 1975
- GLP: no

Results
- No reduced number of foetuses resp. newborn rats in treatment group
- No chromosomal damage occurred in the bone marrow of rats ingesting up to 3 g citric acid/kg bw/day for 5 days.

Conclusions
- Not mutagenic in the reported test
- No mutagenic potential was detected in a dominant lethal assay in rats in which doses of up to 3 g citric acid/kg bw/day were administered for 5 days. A dominant lethal effect is normally reflected by increased early foetal death when treated males are mated with untreated females.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Litton Bionetics Inc 1975a, cited in: BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

15) Genetic toxicity *in vitro* (gene mutations)

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: OECD Guideline 471, „Genetic Toxicology: *Salmonella thyphimurium* Reverse Mutation Assay“
- Type: bacterial reverse mutation assay
- Species/strains: *Salmonella typhimurium* TA 94, TA 98, TA 100, TA 1535, TA 1537
- Metabolic activation: with and without
- Meatbolic activation system: liver homogenate from rats pretreated with polychlorinated biphenyl KC-400
- Concentration: up to 5 mg/plate
- Year: 1984
- GLP: not stated

Results
- Result: no increased incidence of revertant colonies, both with and without metabolic activation

Conclusions
- Not mutagenic in the reported test

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Ishidate et al.: Food Chem. Toxicol 22: 623, 1984

Other
- –

16) Repeated dose toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: > 99 %

Method
- Method: not stated
- Year: 1976
- GLP: no
- Species: rat
- Strain: not stated
- Sex: 10 males and 10 females, average weight = 150 g
- Route of administration: oral, gavage
- Doses: 2,000 mg/kg/day, 4,000 mg/kg/day, 8,000 mg/kg/day, 16,000 mg/kg/day, vehicle only (control group)
- Vehicle: water, with test substance dissolved to attain the respective dose in the same volume administered
- Frequency of treatment: once daily
- Exposure period: 5 days
- Post. obs. period: 10 days, animals were observed for clinical signs, after 10 days survivors were sacrificed

Results
- Results: NOEL = 4000 mg/kg
  LD_{50} = 5600 ± 440 mg/kg/d, identical for males and females

Conclusions
- Low toxicity on repeated oral administration

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- F. Hoffmann La Roche Ltd, unpublished report, 1976

Other
- –

17) Reproductive toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Type: two generation study
- Sex: male + female
- Route of administration: oral, dietary
- Frequency of treatment: daily (feed)
- Exposure period: 90 weeks
- Doses: feed containing 1.2% w/w citric acid, probably ad libitum
- Endpoints: reproduction parameters, blood chemistry, gross pathology, no further details given
- Year: 1956
- GLP: no

Results
- Results: cited as „ ... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed, although a slight increase in dental attrition was reported.“

Conclusions
- No indication for reprotoxicity.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Bonting, Jansen: Voeding 17: 137, 1956; BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

17) Reproductive toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Sex: female
- Route of administration: oral, dietary
- Doses: feed containing 5% w/w citric acid (about 2.5 g/ kg bw/day)
- GLP: no

Results
- No effects on reproduction.
- NOEL = 2500 mg/kg/d

Conclusions
- No indication for reprotoxicity.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Wright, Hughes: Nutr. Rep. Int. 13: 563, 1976; BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

18) Developmental Toxicity/Teratogenicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Sex: males + females, numbers not stated
- Route of administration: not stated, probably oral, feed
- Frequency of treatment: daily
- Exposure period: days 6 to 15 of gestation
- Doses: > 241 mg/kg bw/d
- Year: 1973
- GLP: no

Results
- Results: „No indication of adverse effects on nidation, maternal or fetal survival. The number of abnormalities did not differ from control group.“

Conclusions
- No indication of maternal or foetal toxicity, no teratogenicity reported.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Food & Drug Research Laboratories, Inc.: Teratologic Evaluation of FDA 71-54 Contract no. 71-260, 1973

Other
- –

Human and Environmental Risk Assessment on ingredients of Household Cleaning Products

Substance: Citric Acid and Salts

(CAS# 77-92-9; 5949-29-1; 6132-04-3)

- Edition 1.0 -
April 2005

Table of Contents

1. Substance information

CAS Numbers
This summary covers Citric Acid anhydrous CAS 77-92-9, Citric acid monohydrate CAS 5949-29-1 and Trisodium citrate dihydrate CAS 6132-04-3.

Physical Properties
Citric Acid is a water soluble organic solid with a melting point of approximately 153°C. The acidity of citric acid results from the three carboxylic groups. Having a pKa_1 of 3.13 it is considered as a weak acid.
Citric Acid and its salts undergo dissociation in aqueous media into the citrate anion ($H7C6O7^-$) and the representative cations (H^+, Na^+ and K^+). The chemical structures and available data indicate that the physical-chemical properties, environmental fate behavior, and aquatic and mammalian toxicity of these four compounds mentioned above are similar.

Occurrence
Citric Acid is one of the most widely distributed plant acids and occurs in high concentration in lemon juice (5-7%). It is found in a variety of plants and fruits (especially citrus fruits and berries), leaves, roots etc. Citric acid has a vital function in human and animal metabolism. It appears as an intermediate in the basic physiological citric acid cycle in every eukaryote cell, one of the most important metabolic pathways.

Production and Use
Citric acid has been produced for many years in high volumes and added to processed food and beverages as flavour or stabilizer. It has been used in pharmaceutical preparations, in household cleaners as well as in many special technical applications.

Between 100,000 and 500,0000 tons/annum of citric acid is estimated to have been produced in Europe, including Eastern Europe and Israel, in 1999. Global production is estimated by industry to be approaching 1,000,000 t/a. Worldwide, citric acid production is mainly through microbiological fermentation of molasses and sugar solutions, while extraction from lemon juice or chemical synthesis is negligible. Diluted citric acid from filtered fermentation broths is precipitated with milk of lime (calcium hydroxide) as

practically insoluble calcium citrate, which is then reacted with sulfuric acid to form citric acid and calcium sulfate (gypsum) as a recoverable by-product.
Approximately 50% of the production is estimated to be used by the beverage and soft drinks industry, another 20% in food processing industry and around 10% in pharmaceutical industry, where citric acid is used as an acidulant, buffering agent, taste enhancer and synergist in antioxidant mixtures. Thus, approximately four fifths are destined for human consumption and have a very wide dispersive use. The remainder is split between technical applications in various industries as a complex-forming agent, cleaning agent, softening agent, decalcifying agent, derusting agent, corrosive agent and synergist in antioxidant mixtures; many of those applications also have wide dispersive use, eg, washing powders and detergents. Last, small fractions are used in special applications such as citrate buffering of whole blood samples for transfusion.

Table 1 lists household cleaning applications and typical finished product concentration ranges of Citric Acid (anhydrous and mono-hydrate) and its tri-sodium salt. These figures are based on a survey among 8 detergent manufacturers for the European Union 15+3 (+3 being Iceland, Switzerland and Norway) in 2002. The total consumption in HERA applications is estimated to be at 103,000 tons in 2002 (as Citric Acid).

Table 1:

Product Application	*Range of Citric Acid (anhydrous, monohydrate) and/or its Trisodium Salt in various products.*
Laundry detergents	0-10%
Laundry additives	0-55%
Fabric conditioners	<1%
Machine- / Hand dishwashing detergents	0-45%
Surface Cleaners	0-30%
Toilet Cleaners	0-7%

2. The OECD/ICCA work on Citric Acid / HERA´s conclusion

The member countries of the Organisation for Economic Co-operation and Development (OECD) systematically investigate High Production Volume (HPV) chemicals in order to determine the need for further work on these chemicals. The set of minimum data elements that must be available to draw recommendations is known as the 'Screening Information Data Set' or SIDS. A SIDS Initial Assessment Report (SIAR) for citric acid was presented at SIDS Initial Assessment Meeting (SIAM) 11 in January 2001, and its status was determined to be "currently of low priority for further work"
This Initial Assessment Report (SIAR) is available and accessible at the following address: http://www.chem.unep.ch/irptc/sids/oecdsids/indexcasnumb.htm.

HERA is determined to avoid any duplication of effort and to discourage effort for the sake of only marginal improvements. However, HERA believes that HERA Risk Assessments should be carried out where significant additional risk information can be obtained, and where a refinement of the existing assessments would yield new or significantly different conclusions in particular for the detergent use scenario. A decision which option should be selected has to be taken on a case by case basis.

Human health:
The available data confirm the low acute and (sub)chronic toxicity profile of Citric Acid. The NOAEL for repeated dose toxicity (for rats) is 1200mg/kg/d. It is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. Citric Acid is not mutagenic *in vitro* and *in vivo*, and its sensitising potential is seen as low.
Citric Acid has wide dispersive use, it is naturally present in common fruit and vegetables and is added to processed food and beverages. Potential consumer exposure to citric acid as a consequence of its presence in household laundry & cleaning products is expected to be several orders of magnitude below the rats` NOAEL and of little significance when compared with the normal dietary intake. The available information is judged to be adequate for concluding that the use of citric acid in household laundry and cleaning products raises no safety concerns for consumers.

Environment:
Citric acid is a chemical substance with a very favourable ecological profile. Due to the very low aquatic toxicity and the ready biodegradability, wide dispersive use of citric acid does not present a hazard to the environment.

Several laboratory biodegradation tests (both ready and inherent) show that citric acid and citrate, respectively, is rapidly degraded in both sewage works and surface waters (OECD, 2001; Hoyt and Gewanter, 1992). Available environmental monitoring data show that while raw sewage contains up to 10 mg citrate/l, background concentrations in river water range between <0.04 and maximally 0.2 mg/l (OECD, 2001). It should be kept in mind that these citrate concentrations do not only derive from manmade citric acid, of which the HERA usage accounts for less than 20%, but that citric acid is extremely widespread in nature.

A worst case estimate of the environmental concentrations can be deduced from the available information (see 2.) about the total production figure of citric acid of max.500 000 tons/a in Europe, including Eastern Europe and Israel and a 20% share of wide dispersive use in technical applications. Based on a population figure of ca. 470 million of people (EU-25) and a per capita water consumption of 200 l/day, a raw waste water concentration of 2.9 mg/l can be calculated which shows a good agreement with the mentioned monitoring data.
Conservatively assuming a degree of elimination in WWTP of 87% (based on the figure for readily biodegradable substances provided in Appendix 1 of Part II of the TGD), a WWTP effluent concentration of 0.38 mg/l can be calculated leading to a river concentration of approximately 0.04 mg/l. This figure corresponds again very well to the mentioned few river monitoring data.

In freshwater, citric acid appears to be of low acute toxicity to fish, daphnia and algae, with consistent LC_{50}/EC_{50} values of several hundred milligrams per litre (OECD, 2001). Based on an overview of concrete acute toxicity data of sodium citrate on fish, daphnia and algae (Hoyt and Gewanter, 1992) with an EC50 range of 825 – 1750 mg/l, a PNEC of 0.8 mg/l can be derived (applying an assessment factor of 1000 acc. to TGD). Available (sub)chronic data with a "long-term" daphnia test giving a geometric mean EC_{50} of 98 mg/l and lowest reported EC_0 in cyanobacteria of 80 mg/l (OECD, 2001) support the assumption that the derived PNEC is very conservative.

In spite of the conservativism of this rough exposure and effects assessment, the preliminary risk characterisation shows that the estimated river concentration of citrate is far below the PNEC. Therefore the available information is judged to be adequate for concluding that the use of citric acid in household laundry and cleaning products raises no safety concerns for the environment.

3. THE SIDS INITIAL ASSESSMENT PROFILE

CAS No. 77-92-9

Chemical Name Citric acid

RECOMMENDATIONS
The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health
Based on many experimental data in animals and on human experience, citric acid is of low acute toxicity. The NOAEL for repeated dose toxicity for rats is 1200 mg/kg/d. The major, reversible (sub)chronic toxic effects seem to be limited to changes in blood chemistry and metal absorption/excretion kinetics. Citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. The NOAEL for reproductive toxicity for rats is 2500 mg/kg/d. Further, it is not mutagenic *in vitro* and *in vivo*. Also, the sensitising potential is seen as low. In contrast, irritation, in particular of the eyes but also of the respiratory pathways and the skin, is the major toxicological hazard presented by citric acid; this conclusion is confirmed by a series of reports relating to eye and skin irritation.

Environment
Due to its physico -chemical characteristics citric acid is highly mobile in the environment and will partition to the aquatic compartment. Citric acid is rapidly degraded in both sewage works and surface waters and in soil. Citric acid is of low acute toxicity to freshwater fish, daphnia and algae and also to the few marine species tested; longer -term tests show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria including activated sludge micro-organisms. Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

Exposure
Citric acid is a water soluble organic solid. It is a natural substance that appears as an intermediate in the basic physiological citric acid or Krebs cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes, current global production is estimated to approach 1,000,000 t/a. It has wide dispersive use, being added to processed food and beverages, used in pharmaceutical preparations and in household cleaners as well as in special technical applications.

A large body of physico-chemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old and some located only in standard reference works and reviews. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

NATURE OF FURTHER WORK RECOMMENDED
No further work recommended.

4. References

ECAMA / The European Citric Acid Manufacturers Association http://www.ecama.org

HERA : Guidance Document Methodology, November 2004, Version 7, p. 15-16

HERA : Citric Acid Anhydrous, Citric Acid Monohydrate, Trisodiumcitrate Dihydrate exposure and use data in western Europe for 2002.

H. L. Hoyt, H. L. Gewanter, "Citrate", in O. Hutzinger (ed.), The Handbook of environmental chemistry Vol. 3, Part F, Detergents, Springer-Verlag Berlin Heidelberg 1992, p.229.

OECD SIDS, SIAM 11, 23-26 January 2001, Unep Publications, SIAR Citric Acid http://www.chem.unep.ch/irptc/sids/oecdsids/indexcasnumb.htm.

U.S. High Production Volume (HPV) Chemical Challenge Program, Assessment Plan for Acetic Acid and Salts Category, prepared by American Chemistry Council Acetic Acid and Salts Panel, June 28, 2001
http://www.epa.gov/chemrtk/acetisalt/c13102tc.htm

Römpp Encyclopedia Natural Products, Georg Thieme Verlag Stuttgart, 2000,
ISBN 3-13-117711-X (GTV)

5. Contributors

This dossier has been prepared by the HERA Secretariat on behalf of the ECAMA, the European Citric Acid Manufacturer Association and its member companies.
Additional input was provided by the experts of the HERA (Environment and Human Health) Task Forces. Volume and exposure information for the use of household detergents and cleaners was gathered among the HERA Formulator Companies and has been aggregated by the Cefic Statistical Service department.

Attachment 5

SIDS Initial Assessment Report

For

SIAM 5

Belgirate, Italy, 28-30 October 1995

1. Chemical Name: Sodium dodecyl sulphate

2. CAS Number: 151-21-3

3. Sponsor Country: Germany
SIDS Contact Point in Sponsor Country: Dr. Reiner Arndt

4. History SIDS Dossier and Testing Plan were reviewed in September 1993, where the following SIDS Testing Plan was agreed:

No testing	(X)
Testing	( )

The SIAR was discussed at the 2nd SIAM in July 1994 and a revised version was reviewed at SIAM 5 in 1995.

5. Date of Submission: June 1995

6. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	151-21-3
Chemical Name	Sodium dodecyl sulfate (SDS)
Structural Formula	CH_3-$(CH_2)_{11}$-O-$SO_3^-Na^+$

RECOMMENDATION OF THE SPONSOR COUNTRY

Based on an initial assessment of the effect and exposure data provided in the SIDS dossier, the chemical can be considered to present a low potential for risk to man and the environment. Thus there is no current priority for undertaking post-SIDS testing and/or exposure analysis or an in-depth assessment.

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

The production volume of SDS is ca. 10,000 t/a in Germany. SDS is used as a surfactant in detergents, dispersants, cosmetics and toiletry. SDS is classified as "readily biodegradable" with "low bioaccumulation". The most sensitive environmental species to SDS is the clam *Corbicula fluminea* (30d-NOEC = 0.65 mg/l).
All relevant toxicity endpoints are covered. SDS is a substance of low toxicity. The substance did not induce mutations in different test systems. The lowest NOAEL was established for repeated dose toxicity, being 100 mg/kg bw/day.

The aquatic local PEC was estimated to be 2.3 µg/l, additional to a "background" regional PEC of further 2.3 µg/l.
It is calculated that adult consumers may be exposed to up to 0.030 mg/kd/day and that babies may be exposed to 0.034 mg/kg/day. The highest consumer exposure, however, is estimated to occur to children, with the ***worst case*** exposure being 0.160 mg/kg/day. Babies (ca. 0.25 mg/kg/day) and adults (ca. 0.05 mg/kg/day) are exposed to a lesser extent. Occupational exposure is calculated to be about 0.100 mg/kg/day, and the combined consumer and occupational exposure for workers is about 0.130 mg/kg/day.

Based on the NOEC of 0.65 mg/l, a risk to the aquatic compartment is not to be expected.
A safety margin for ***worst case*** human exposure (children) of > 600 was established in the risk assessment. Taking into account the quality and quantity of the toxicological data and the kind of health effects observed (mild hepatotoxicity), a safety margin of > 600 is considered sufficient. Therefore, it is concluded that sodium dodecyl sulfate is of no concern with respect to human health.

NATURE OF FURTHER WORK RECOMMENDED

none

Full SIDS Summary

CAS-NO.: 151-21-3		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMICAL				
2.1	Melting Point		NA	204-207 °C
2.2	Boiling Point		/	
2.3	Density		NA	400-600 kg/m^3
2.4	Vapour Pressure		/	
2.5	Partition Coefficient (Log Pow)		NA (calc)	1.6
2.6 A	Water solubility		NA	150000 mg/l at °C
B	pH			6-9 at 10 g/l at 20 °C
	pKa		/	/
2.12	Oxidation : Reduction potential		/	/ mV
ENVIRONMENTAL FATE / BIODEGRADATION				
3.1.1	Photodegradation		ND	In air $T_{1/2}$ = / hour
3.1.2	Stability in water		ND	$T_{1/2}$ = / min
3.2	Monitoring data		/	
3.3	Transport and Distribution		estimated NA NA	preferred compartment: hydrosphere BCF: 2.1 - 7.1 water-sediment: K = 70 - 100 l/kg
3.5	Biodegradation		OECD 301 OECD Conf. test OECD 303A	readily biodegradable elimination > 99% elimination > 96%
ECOTOXICOLOGY (lowest effect concentrations only)				
4.1	acute/prolonged toxicity to fish	Macrones vittatus	NA	LC_{50} (96 hr) = 1.39 mg/l
		Menidia beryllina	EPA-600/4-87/028 (larvae)	LC_{50} (7 d) = 1.8 mg/l
		Saccobranchus fossilis	NA	NOEC (60d) = >= 2.24 mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates (daphnia)	Homarus americanus	NA	EC_{50} (96 hr) = 0.72 mg/l
		Brachionus rubens	EPA-600/4-85/013	EC_{50} (24 hr) = 1.35 mg/l
		Corbicula fluminea	NA	NOEC (60d) = 0.65 mg/l
4.3	toxicity to aquatic plants e. g. algae	Sel. capri-cornutum	NA	EC50 (8 d) = 3.75 mg/l
		Champia parvula	EPA-600/4-87/028	EC_{50} (48 hr) = 0.3 mg/l

CAS-NO.: 151-21-3		SPECIES	PROTOCOL	RESULTS
ECOTOXICITY				
4.4	toxicity to microorganisms	Photobact. phosphoreum Uronema parduczi	Microtox NA	EC_{50} (15 min) = 0.38 mg/l TT (EC3) (20h) = 0.75 mg/l
4.5.2	chronic toxicity to aquatic invertebrates (daphnia)	Daphnia magna	EPA-600/3-75-009	NOEC (40d) = 2 mg/l
4.6.2	toxicity to terrestrial plants	Cicer arietinum	NA	EC_{50} (48 hr) = 361 mg/l
TOXICOLOGY				
5.1.1	acute oral toxicity	rat	NA	LD_{50} = 1200 mg/kg
5.1.3	acute dermal toxicity	rabbit guinea pig	NA NA	LD_{50} = ca. 600 mg/kg LD_{50} = >1200 mg/kg
5.4	repeated dose toxicity	rat	NA	NOAEL =100 mg/kg/day (hepatotoxicity)
5.5	genetic toxicity in vitro			
	bacterial test (gene mutation)	S. typhimurium	Ames test	negative (with and without metabolic activation)
	non-bacterial test (gene-mutation)	mice	Lymphoma cell forward mutation assay	negative (with and without metabolic activation)
	non-bacterial test (indicator test for gene and/or chromosome mutation)	Chinese hamster	Sister chromatid exchange	negative (with and without metabolic activation)
5.6	genetic toxicity in vivo (chromosome aberration)	rat	Micronucleus assay	negative
5.8	toxicity to reproduction	mice		NOAEL = 1000 mg/kg/day (male fertility)
5.9	developmental toxicity / teratogenicity	mice rabbits		NOAEL ≤ 300 mg/kg/day (maternal toxicity) NOAEL = 400 mg/kg/day (resorption/litter loss) NOAEL =600 mg/kg/day (foetal malformation)
5.11	experience with human exposure	In experimental ulcer treatment up to 80 mg/kg/day (highest dose tested) were tolerated without adverse side effects. Up to 1 % are considered safe for cosmetic non-rinse-off products.		

SIDS Initial Assessment Report

1.IDENTITY

Name:	Sodium dodecyl sulfate
Synonyms:	Sodium lauryl sulfate SDS Sulfuric acid, monododecyl ester, sodium salt
CAS Nr.:	151-21-3
Empirical Formula:	$C_{12}H_{26}O_4S.Na$
Structural Formula:	CH_3-$(CH_2)_{11}$-O-$SO_3^-Na^+$
Purity of industrial product:	Sodium dodecyl sulphate is commercially available as solids (powder or needles) of > 90 % purity. Technical-grade sodium lauryl sulphate is commercially available as solution of variable solid content. It has a purity of about 70%, with respect to the dry material.
Impurities:	Linear alkyl sulphates of shorter and longer chain length, the main impurity being the C14-compound

2. EXPOSURE

2.1 General discussion

Sodium dodecyl sulphate is used in general as detergent, as dispersant, and as surfactant. Pure sodium dodecyl sulphate is used mainly in dentifrice products, in hair shampoos, and in emulsion polymerisation (4). The rest is either used in special cosmetic formulations, e.g. for bubble baths and hair bleaches, or as a fine chemical, e.g. as denaturing agent in gel electrophoresis (25). Besides pure sodium dodecyl sulphate detergent manufacturers usually produce "technical grade" sodium dodecyl sulphate, too, a product that consists of approximately 70 % sodium dodecyl sulphate and 30 % sodium tetradecyl sulphate. This product is generally called sodium lauryl sulphate. It is described by the IUPAC-name sulfuric acid, mono-C12-14-alkyl esters, sodium salts and the CAS-No. 85586-07-8. Due to the chemical, toxicological, and ecological similarity of the technical grade sodium dodecyl sulphate and pure sodium dodecyl sulphate it is recommendable to assess both substances together (2, 24). Technical grade sodium dodecyl sulphate is used as detergent in dish-washing products (main use), as additive for plastics and latices, and in paints and lacquers (4).

The production volume for pure (> 95 % C_{12}) sodium dodecyl sulphate is estimated as follows. Based on a market volume of 42,600 t for dentifrice products in 1992 published by the German Bureau of Statistics (1) and an average concentration of 2 % of the substance in these products, an amount of 850 t is calculated for this application. The potential exposure from hair shampoos is estimated on the basis that only the hair shampoos from US companies contain sodium dodecyl sulphate (up to 8 %), whereas the corresponding domestic products do not contain this substance. Given that the US products account for 1/3 of the German market and a market volume of 94,200 t

for these products (1) and further assuming an average concentration of 5 % sodium dodecyl sulphate in the US shampoos, a volume of 1,500 t is calculated for this product group. In addition, about 1,500 t are used in emulsion polymerisation for the production of polyvinyl chloride, synthetic rubber and other polymers (28). Taken all three fields of application into account it is estimated that a total of 4,000 t of pure sodium dodecyl sulphate are used annually in Germany.

The production volume for technical grade sodium dodecyl sulphate in Germany is not known. On the basis of the German Statistics on Trade and Captive Use of fatty alcohole sulphates in total (ca. 33,000 t in 1993) and the assumption that 30 % of this quantity is sodium lauryl sulphate, it is estimated that ca. 10,000 t per year of sodium lauryl sulphate (pure and technical grade together) are produced in Germany (3). By subtracting the 4,000 t of pure sodium dodecyl sulphate mentioned above, a production volume of 6,000 t is calculated for the technical product. Therefore, a total exposure of about 10.000 t of sodium lauryl sulphate has to be considered for Germany.

Whereas the pure sodium dodecyl sulphate is produced as a dry material (i. e. powder or granules) for which dust formation is of concern, the technical grade sodium dodecyl sulphate is mainly produced as a paste or as solutions. Therefore, occupational exposure by inhalation is of relevance only for the high purity dodecyl sulphate. Due to its broad use in consumer products it is expected that most of the substance will ultimately end up in the environment (see below).

According to a preliminary exposure profile in the USA, the production of SDS is estimated at ca. 90,000 t/a. Its primary use is in the cosmetics/personal care products industry (24).

2.2 Environmental exposure

2.2.1 General/Environmental fate

SDS is highly soluble in water (150 g/l). The vapour pressure is not known, but due to its tensioactive property, volatilisation from water is not to be expected.
Bioaccumulation factors between 2.1 and 7.1 have been determined experimentally in several tests. Recorded clearance times ct_{50} were 100 and 72 h. Different exposure concentrations had no effect upon the BCF. Bioaccumulation is therefore considered to be low.

Adsorption on sediment was studied and sediment-water partition coefficients of 70.2 l/kg and 99.1 l/kg were determined. The organic carbon content of the sediment being 22.2%, Koc-values of 320 and 450 l/kg can be deduced, although it is not clear if SDS adsorbs on organic or mineral matter.
Because of the adsorption of SDS onto sediment, a partitioning between the water phase and the suspended matter would have to be considered. Assuming the above determined partition coefficient to be representative, and with a typical concentration of suspended matter of 15 mg/l, the concentration in the water phase would be diminished by less than 1%. It can therefore be neglected for the PEC-calculations below.

According to the data described above, the preferred environmental compartment is the hydrosphere (SDS being a tenside, a calculation with a fugacity model is not opportune).

SDS has proven to be readily biodegradable in several standard tests (OECD GL 301).
Furthermore in the OECD Confirmatory Test, elimination rates of ca. 99 % were reached. In the Coupled Unit Test (OECD GL 303A), removal rates of >99% for an influent concentration of 20 mg/l and of 96% for 100 mg/l were reached.
SDS is also degradable under anaerobic conditions with digester sludge (ca 91 % after 28 days).

According to the EU-Technical guidance Document (16), the results from the Coupled Units Test can be used for real WWTPs. In the following exposure assessment, an elimination rate of 99% in WWTPs will be assumed.

In a river water die away test, 100% degradation (probably primary degradation) was reached after ca. 3 days at 10 °C. At higher temperatures the disappearance time was even shorter. For the exposure assessment, a worst case half-life of 3 days will be estimated i.e. assuming a first order kinetic, the degradation rate constant k = 0.23 d^{-1}.

2.2.2 Exposure assessment

2.2.2.1 Hydrosphere

a) local exposure

- during production

During production in Germany, the emission of SDS into waste water is not known. Assuming that 0.5 % of 10000 t are annually released, and with an elimination factor of 99% in the WWTP, 500 kg/a are released into the river Rhine (near the production site). According to the producer, SDS is not continually produced. Assuming a production period of 180 d/a, and with a low flow of 690 m^3/s (10-percentile) of the Rhine, a resulting **PEC_{local} of 46 ng/l** is calculated.

In the USA, based on data submitted by the producers, the concentrations in the WWTP-effluents were estimated to be < 0,96 µg/l. As all the production sites were releasing their effluents into coastal saltwater bodies, no instream dilution could be calculated. With a default dilution factor of 10, a **PEC_{local} of < 96 ng/l** is estimated.

- during use

As the exact quantitative use pattern is not known, it is assumed that the production volume of 10000 t/a in Germany are emitted diffusely with domestic waste water into the hydrosphere.
Considering an average per-capita waste water discharge of 150 l/day and a population of about 80 millions, the concentration in the raw sewage is

$$C = \frac{10^{10}\ g}{4.38 \cdot 10^{12}\ l} = 2.28\ mg/l$$

On a local scale, it is assumed that the household sewage will be purified in biological treatment plants, and the dilution factor during release into the receiving stream will be 1:10. The local concentration is calculated:

$$\mathbf{PEC_{local}} = \frac{2280\ \mu g/l \cdot (1-0.99)}{10} = \mathbf{2.3\ \mu g/l}$$

b) regional exposure

For the calculation of the regional PEC the use of a fugacity model is not opportune due to the ionic nature of SDS. The regional concentration can be estimated in a first approach with the following formula (30):

$$PEC_{regional} = \frac{EMIS}{FLOW + Vk}$$

with: EMIS: emission into surface water
FLOW: flow through the water compartment
V: Volume of water compartment
k: first order biodegradation rate constant (0.23 d^{-1})

The default values described in (16) will be used for the calculation:
- a small but densely populated area is considered: 200 x 200 km with 20 million inhabitants;
- the used amount of SDS, calculated on a per-capita basis for this area would be 2500 t/y;
- a WWTP connection rate of 80% is used so that:

EMIS = 0.2 x·2500 + 0.8·(1-0.99)·2500 = 520 t/y

- with an area fraction of water of 0.02 and a mixing depth of 3 m, V = 2.4 x10^9 m^3
- with an average residence time of the water of 40 days, FLOW = 6 x 10^7 m^3/d

=> **$PEC_{regional}$ = 2.3 µg/l**

c) total aquatic exposure

Estimating the total burden in surface waters, the $PEC_{regional}$ is considered as a background concentration in surface waters. Locally, therefore the PEC_{local} and the $PEC_{regional}$ are added to reflect the maximum concentration in surface waters.

=> **$PEC_{aqua} = PEC_{regional} + PEC_{local}$ = 2.3 + 2.3 = 4.6 µg/l**

2.2.2.2 Soil compartment

The main release route of SDS into the soil compartment would be through spreading of sewage sludge.

Assuming the Koc-value of 450 l/kg to be valid and with an organic carbon content of sewage sludge of 40 %, the waste water concentration of 2.28 mg/l results in a sludge concentration of 410 mg/kg dw.

As SDS is also anaerobically biodegradable, the concentration would probably be significantly decreased during the processing of the sewage sludge in the digester. However, this process cannot be quantified.

Assuming an application of 1.7 t sludge/y for agricultural land (22) over an average depth of 20 cm top soil layer and of 1 t/a for grass-land over an average depth of 10 cm, the initial concentration in soil can be estimated (soil bulk density is considered to be 1500 kg/m^3):

$PEC_{arable\ land}$ = 410·1.7/3000 = 0.232 mg/kg dw

$PEC_{grass\ land}$ = 410·1/1500 = 0.272 mg/kg dw

This is probably an overestimation, since the anaerobic degradability with digester sludge (91% after 28 days) could not be taken into consideration. In countries, where higher application rates are allowed, higher concentrations can be expected.

For the calculation of the concentration in the pore water, an organic carbon content in the soil of 2% is assumed. With the Koc-value of 450, the concentration is:

$PEC_{arable\ land} = 0.232/(450 \cdot 0.02) = 26\ \mu g/l$

$PEC_{grass\ land} = 0.272/(450 \cdot 0.02) = 30\ \mu g/l$

As SDS is also biodegradable in soil, this initial concentration is expected to decrease rapidly, so that an accumulation in soil with repeated application is not probable.

2.3 Consumer exposure

The objective of any human exposure assessment (consumer and/or occupational) is to calculate a "realistic" Estimated Human Exposure (EHE) level, expressed in terms of dose per body weight per time, e.g. mg $kg^{-1}day^{-1}$. The level of exposure has then to be compared with the results obtained from conducting the Initial Assessment of Health Effects on the basis of the approved SIDS dossier, and a final judgement has to be made as to whether the chemical presents a cause for concern or not. For consistency within assessments the following standardized physiological parameters are to be used:

(a) body weights: adult = 70 kg, child = 15 kg, baby = 5 kg

(b) respiratory volume = 1.3 m^3 per h (16)

Due to the fact that sodium dodecyl sulphate is used in very different typs of products (see EUCLID dataset, chapter 1.7), different paths of potential consumer exposure have to be assessed. Reviews of consumer exposure can be found in (25) and (26).

2.3.1 Dermal consumer exposure

Sources of dermal exposure to sodium dodecyl sulphate for consumers are on one hand hair shampoos, cleansing products, and dish-washing formulations. These applications are, however, considered to be of less relevance, due to the short exposure times which usually are < 15 min, and the diluted application. A different situation might exist for leave-on products like cosmetic creams and moisturizing lotions that remain in contact with the skin for prolonged time. Because of the potentially irritating effects of sodium dodecyl sulphate (see chapter 5.11 in ref. 4), leave-on products produced in Germany do not contain sodium dodecyl sulphate anymore. For these applications sodium dodecyl sulphate is nowadays substituted by substances that have a better skin compatibility. However, it can not be excluded that consumers come in contact with products of other origin that still contain this substance. Therefore, the question ”To what extent can sodium dodecyl sulphate penetrate the skin during prolonged contact?” has to be answered.

In vitro it was found that human skin is about three times less permeable for sodium dodecyl sulphate than rat skin (6). In addition it was found that increasing levels of sodium dodecyl sulphate from transdermal permeation appeared only after prolonged time. In another study time- and concentration-dependencies were investigated on human skin using ^{35}S-labelled sodium lauryl sulphate (7). Again, with time increasing penetration rates were found. This penetration pattern is probably related to the irritating effects of sodium dodecyl sulphate which, depending on

concentration and contact time can lead to skin damage and increased permeability of the skin (9). The test conditions used in the in vitro studies were, however, not use-related. In contrast to the in vitro experiments, it was shown in in vivo studies with rats that only 0.5% of radiolabelled sodium dodecyl sulphate penetrates intact skin within 24 hours (8). Obviously, the Stratum Corneum is a very effective barrier. Because the study of Greb et al. (8) was done under typical use conditions, it is considered the most relevant one. On the basis of these data it is assumed that under use conditions approx. 0.5 % of the sodium dodecyl sulphate applied may penetrate the skin barrier per day.

As a worst case scenario the use of a body lotion containing 1 % sodium dodecyl sulphate is considered. For adults a whole body application of 7.5 g body lotion (16) and a 24 h penetration rate of 0.5 % is assumed. For children the application of 3.5 g body cream, and for babies of 1.5 g body cream is assumed. The Estimated (transdermal) Human Exposure to sodium dodecyl sulphate resulting from application of a cream is calculated as follows:

Quantity applied (Q) = **7,500 mg (for adults)**

" = **3,500 mg (for children)**

" = **1,500 mg (for babies)**

Weight fraction (WF) = **1 % (= 0.01)**

Duration of exposure(DUR) = **24 h/day**

Penetration rate (PR) = $\frac{\textbf{0.5 \%}}{\textbf{24 h}}$

Body weight (BW) = **Adult 70 kg**
" **Child 15 kg**
" **Baby 5 kg**

$$\textbf{EHE}_{\textit{dermal}} = \frac{\textbf{Q x WF x DUR x PR}}{\textbf{BW}}$$

$$\textbf{EHE}_{\textit{dermal, adults}} = \frac{\textbf{7,500 mg x 0.01 x 24 h x 0.005}}{\textbf{24 h x day x 70 kg}}$$

$$\textbf{EHE}_{\textit{dermal, children}} = \frac{\textbf{3,500 mg x 0.01 x 24 h x 0.005}}{\textbf{24 h x day x 15 kg}}$$

$$\textbf{EHE}_{\textit{dermal, babies}} = \frac{\textbf{1,500 mg x 0.01 x 24 h x 0.005}}{\textbf{24 h x day x 5 kg}}$$

$\textbf{EHE}_{\textit{dermal, adults}}$ = **0.0053 mg $kg^{-1}day^{-1}$**

$\textbf{EHE}_{\textit{dermal, children}}$ = **0.0117 mg $kg^{-1}day^{-1}$**

$\textbf{EHE}_{\textit{dermal, babies}}$ = **0.015 mg $kg^{-1}day^{-1}$**

2.3.2 Oral intake for consumers

Three paths of oral ingestion of sodium dodecyl sulphate are considered:

- via contaminated drinking water
- via contaminated food
- via personal care products

2.3.2.1 Intake from contaminated drinking water

The upper limit for anionic surfactants in drinking water set by the World Health Organization (WHO) is 0.2 ppm. European countries adopted similar regulations. For example the German Drinking Water Regulation has the same upper limit of 0.2 ppm. In 1973 the European Economic Community (EEC) passed a directive which prohibits the use of detergents that are less than 90 % biodegradable (10). As a consequence, biodegradable anionic surfactants were introduced in the market. This resulted in a significant drop of the amounts of anionic surfactants in surface waters. Sodium dodecyl sulphate as a matter of fact is degraded > 99 % within 3 - 30 days, depending on the conditions (see chapter 2.2.1).In chapter 2.2.2.1 a total concentration of 4.6 µg/l was estimated for surface waters.

As a worst case scenario a concentration of sodium dodecyl suphate in the drinking water of 4.6 µg/l is assumed, implying that no elimination occurs during treatment of drinking water. Further, it is assumed that there is a complete intestinal absorption. The daily human water intake is assumed to be two liters for adults, 1.5 liters for children, and 0.6 liters for babies. The Estimated Human Exposure is then calculated as follows:

$$\mathbf{EHE}_{\textit{oral, water}} = \frac{\textbf{concentration x percentage x volume}}{\textbf{body weight}}$$

$$\mathbf{EHE}_{\textit{oral, water (adults)}} = \frac{\textbf{0.0046 mg/l x 2 l/day}}{\textbf{70 kg}} = \textbf{0.00013 mg kg}^{-1}\textbf{day}^{-1}$$

$$\mathbf{EHE}_{\textit{oral, water (children)}} = \frac{\textbf{0.0046 mg/l x 1.5 l/day}}{\textbf{15 kg}} = \textbf{0.00046 mg kg}^{-1}\textbf{day}^{-1}$$

$$\mathbf{EHE}_{\textit{oral, water (babies)}} = \frac{\textbf{0.0046 mg/l x 0.6 l/day}}{\textbf{5 kg}} = \textbf{0.00055 mg kg}^{-1}\textbf{day}^{-1}$$

The estimates given above are based on worst-case assumptions and probably over-estimate the indirect human exposure via drinking water. In an independent survey undertaken on behalf of the US-EPA it was estimated that the maximum exposure via drinking water is 2.6 mg/year, i.e. 0.0001 mg $kg^{-1}day^{-1}$ for adults (24).

2.3.2.2 Intake from contaminated food

Oral intake can occur with food that contains trace levels of sodium dodecyl sulphate. The highest intake may occur in bottle-fed babies and infants from contaminated milk powder. It is reported in the literature (13), that up to 10 ppm anionic surfactant may be present in milk powder. As an exposure scenario it is assumed that 10 % of the milk powder used is contaminated. Assuming that babies on average drink 600 ml of milk per day, that the milk powder concentration is 15 % w/v, and that all anionic surfactant is sodium dodecyl sulphate, the calculated intake via this route is:

$$\mathbf{EHE_{oral,\ milk} = \frac{WF \times F \times C \times M}{body\ weight}}$$

Where Weight fraction (WF) = 10 ppm = 10 mg kg^{-1}

Contaminated fraction (F) = 0.1

Concentration of milk powder (C) = 15 %

Milk consumption (M) = 0.6 kg day^{-1}

$$\mathbf{EHE_{oral,\ milk} = \frac{10\ mg\ kg^{-1} \times 0.1 \times 0.15 \times 0.6\ kg\ day^{-1}}{5\ kg}}$$

$EHE_{oral,\ milk}$ = 0.018 mg $kg^{-1}day^{-1}$ (babies only)

Another route of oral exposure that has to be considered is contaminated fish and seafood. In a survey undertaken on behalf of the US-EPA it was estimated, that the maximum exposure via contaminated fish may be as high as 149 mg/year, i.e. 0.006 mg kg^{-1} day^{-1} for adults (24).

$EHE_{oral,\ fish}$ = 0.006 mg $kg^{-1}day^{-1}$ (adults and children)

A special exposure path may exist for Japanese, because in Japan the use of anionic surfactants is wide-spread for cleaning of food and vegetables. In 1974 the Japanese Soap and Detergent Industry Association summarized the daily intake of anionic surfactants from detergent-washing of food to be 0.016 mg kg^{-1} day^{-1} (12). Given that 30 % of anionic surfactant used for this purpose is sodium dodecyl sulphate, an exposure of 0.005 mg kg^{-1} day^{-1} results for this route.

$EHE_{oral,\ deterg\text{-}wash}$ = 0.005 mg $kg^{-1}day^{-1}$ (adults and children)

This path, however, is probably limited to Japan and of no relevance for other countries.

2.3.2.3 Oral intake from personal care products

Another field of consumer exposure is the use of sodium dodecyl sulphate containing personal care products like toothpastes and mouth rinses. Sodium dodecyl sulphate is one of the most widely used synthetic detergent in dentifrices. Usually, toothpaste is in contact with the mucous membranes only

for a short time (< 3 min), and then is rinsed off with plenty of water. However, some residual detergent dissolved in the saliva is regularly swallowed. It is estimated that adults ingest 1-2 % of the toothpaste used. Children on the other hand may occasionally swallow as much as 30-40 % of the toothpaste (11). As a case scenario for the long-term oral intake of sodium dodecyl sulphate by means of dentifrices it is assumed that 1.5 g of toothpaste are used two times per day, that 1.5 % of the toothpaste are regularly swallowed by adults, and that children on average ingest up to three times more toothpaste than adults (14). Thus, it can be estimated that adults have a daily intake of 45 mg toothpaste and children have a daily intake of 135 mg toothpaste. It is further assumed that toothpaste contains on average 1.5 % sodium dodecyl sulphate. Calculated for average body weights of 70 kg (adult) and 15 kg (child), respectively, the corresponding Estimated Human Exposure values are:

$$\mathbf{EHE}_{oral,\ dentif.} = \frac{\text{amount ingested x concentration}}{\text{body weight}}$$

$$\mathbf{EHE}_{oral,\ dentif.,(adult)} = \frac{45\ mg\ day^{-1} \times 0.015}{70\ kg} = 0.010\ mg\ kg^{-1}day^{-1}$$

$$\mathbf{EHE}_{oral,\ dentif.,(child)} = \frac{135\ mg\ day^{-1} \times 0.015}{15\ kg} = 0.135\ mg\ kg^{-1}day^{-1}$$

2.3.3 Inhalation

Due to the fact that consumer products containing sodium dodecyl sulphate are almost exclusively liquids or creams but not powders, dust formation and hence inhalation is not considered as a relevant exposure path for the public.

$$\mathbf{EHE}_{inhal.} = 0$$

2.3.4 Total daily intake for consumers

For the case of simultaneous dermal exposure by means of a body lotion and oral intake by means of contaminated water/food and the use of dentifrices the resultant total Estimated Human Exposure values for babies, children and adults are given below:

$$\mathbf{EHE}_{consum,(adults\ and\ children)} = \mathbf{EHE}_{dermal} + \mathbf{EHE}_{oral,water} + \mathbf{EHE}_{oral,deterg.wash} + \mathbf{EHE}_{oral,\ fish} + \mathbf{EHE}_{oral,\ dentif.}$$

$$\mathbf{EHE}_{consum,\ (babies)} = \mathbf{EHE}_{dermal} + \mathbf{EHE}_{oral,\ water} + \mathbf{E}_{oral,\ milk}$$

$$\mathbf{EHE}_{consum,\ (adults)} = (0.0053+0.00013+0.005+0.006+0.01)\ mg\ kg^{-1}day^{-1} = 0.026\ mg\ kg^{-1}day^{-1}$$

$$\mathbf{EHE}_{consum,\ (children)} = (0.0117+0.00046+0.005+0.006+0.135)\ mg\ kg^{-1}day^{-1} = 0.158\ mg\ kg^{-1}day^{-1}.$$

$$\mathbf{EHE}_{\textit{consum, (babies)}} = \mathbf{(0.0150+0.00055+0.018)\ mg\ kg^{-1}day^{-1}}$$
$$= \mathbf{0.034\ mg\ kg^{-1}day^{-1}}$$

2.4 Occupational exposure

2.4.1 Exposure at the work place

Information on occupational exposure is only available on a company level. Sodium dodecyl sulphate is normally produced by reaction of dodecanol either with chlorosulphuric acid or gaseous sulphur trioxide in a closed reaction vessel. For the production of solid products, the sodium dodecyl sulphate slurry is then spray-dried. The only steps that could lead to occupational exposure are sampling for quality control analyses and baging of the final product. In general, the substance is not produced continuously, but in batches at about 90 days during the year (29). For consistency within assessments the following standardized physiological parameters were used (16):

average body weight of workers = 70 kg
respiratory volume = 1.3 m^3 / h

2.4.1.1 Inhalation

Exposure to sodium dodecyl sulphate dust can occur only during handling of the powdered cosmetic grade products which are used as ingredient for the above mentioned consumer products, e.g. during blending of the substance. Data on concentration of sodium dodecyl sulphate in the air are available from only one production site (15). Maximum dust concentrations of 1.0 and 1.6 mg/m^3 were determined from the area where the powdered product is filled in bags, the average of 13 measurements being 0.66 mg/m^3. As a worst case scenario the maximum dust concentration of 1.6 mg/m^3 was chosen. Further, it was assumed that all dust is sodium dodecyl sulphate, and that the material is fully respirable according to the Johannisburg Convention. The respiratory volume of workers is assumed to be 1.3 m^3 per hour (16). The average long-term Estimated Human Exposure from inhalation of sodium dodecyl sulphate dust at the workplace is then calculated as follows:

$$\mathbf{EHE}_{\textit{respirat.,}} = \frac{\mathbf{PDR}}{\mathbf{body\ weight}}$$

Where $\mathbf{PDR}_{\textit{respirat.}}$ = **annual rate for inhalative potential dose (mg/year)**

$$\mathbf{PDR}_{\textit{respirat.}} = \mathbf{CONC \times IH \times DUR \times FREQ}$$

Where
CONC = **Concentration of substance in the air (mg/m^3)**
IH = **Inhalation rate (m^3/h)**
DUR = **Duration of exposure (h)**
FREQ = **Frequency of events per year (events/year)**

$$\mathbf{PDR}_{\textit{respirat.}} = \frac{\mathbf{1.6\ mg\ m^{-3} \times 1.3\ m^3\ h^{-1} \times 8\ h \times 90}}{\mathbf{year}}$$

$PDR_{respirat.}$ = 1,500 mg/year

$$EHE_{respirat.} = \frac{1{,}500\ mg}{365\ day \times 70\ kg} = 0.059\ mg\ kg^{-1}day^{-1}$$

2.4.1.2 Dermal workplace exposure

Due to the small surface area of the uncovered and therefore potentially exposed skin compared to the inner surface area of the lungs, and the barrier function of the Stratum Corneum it is expected that dermal exposure is less a problem than inhalation. For a worst case scenario it is assumed that a worker caused excessive dust formation (>> 1.6 mg m^{-3}) due to careless handling of the substance, and that he did not wear protective clothing and therefore got exposed on head and both hands. The surface of the exposed skin is assumed to be 2,020 cm^2 (for head and hands), and the dust adherence to the skin should be 3.44 mg cm^{-2} (16). Further, a skin penetration rate of 0.5 % in 24 h is assumed (see chapter 2.3.1). With a contact time of 8 h the Estimated Human Exposure from occupational skin contact is calculated as follows:

$$EHE_{dermal} = \frac{PDR \times penetration\ rate \times contact\ time}{body\ weight}$$

Where PDR = annual rate for dermal potential dose (mg/year)

PDR = WF x AV x DA x FREQ

Where
WF = Weight fraction of substance in product (unitless)
AV = Skin surface area exposed per event (cm^2/event)
DA = Dust adherence (mg/cm^2)
FREQ = Frequency of events per year (events/year)

PDR = 1 x 2,020 cm^2 x 3.44 mg cm^{-2} x 90
PDR = 625,400 mg/year

$$EHE_{dermal} = \frac{PDR \times PR \times DUR}{BW}$$

Where
PR = Penetration rate (0.005/24 h)
DUR = Duration of exposure (8 h)
BW = Body weight (70 kg)

$$EHE_{dermal} = \frac{625400\ mg \times 0.005 \times 8\ h}{365\ day \times 70\ kg \times 24\ h} = 0.04\ mg\ kg^{-1}day^{-1}$$

Remark: The amount of substance supposed to be in contact with the skin seems to be a vast overestimation because it is based on the assumption that the workers are not protected and that excessive dust formation occurs each time the substance is produced.

2.4.1.3 Total occupational exposure

The total exposure to sodium dodecyl sulphate at the workplace is given by the exposure that resulted from inhalation combined with the exposure that resulted from dermal contact.

$$\mathbf{EHE}_{\textit{occupational, av.}} = \mathbf{EHE}_{\textit{respirat.}} + \mathbf{EHE}_{\textit{dermal}}$$

$$\mathbf{EHE}_{\textit{occupational, av.}} = \mathbf{0.059} + \mathbf{0.04} = \mathbf{0.100\ mg\ kg^{-1}day^{-1}}$$

Remark: The total Estimated Human Exposure calculated above is considered to be a worst case scenario. It assumes that the workers are not protected by masks and gloves. Under normal circumstances, however, the workers are protected. This would reduce the total occupational exposure by at least an order of magnitude.

2.4.2 Combined consumer and occupational exposure of workers

In contrast to the general public for which only one aspect of exposure (consumer exposure) is of concern, workers may be at risk of combined occupational ***and*** consumer exposure. Therefore, the total Estimated Human Exposure for workers is calculated as:

$$\mathbf{EHE}_{\textit{(worker, total)}} = \mathbf{EHE}_{\textit{consum}} + \mathbf{EHE}_{\textit{occupational}}$$

$$\mathbf{EHE}_{\textit{(worker, total)}} = \mathbf{0.026} + \mathbf{0.100} = \mathbf{0.126\ mg\ kg^{-1}day^{-1}}$$

3. TOXICITY

3.1 Human toxicity

3.1.1 Acute toxicity

Oral	:	rat, LD_{50}	=	1,200 +/- 300 mg/kg
Inhalation	:		=	no data available
Dermal	:	rabbit, LD_{50}	=	ca. 600 mg/kg
		guinea pig, LD_{50}	=	> 1,200 mg/kg
i. p.	:	rat, LD_{50}	=	ca. 200 mg/kg
		mouse, LD_{50}	=	ca. 250 mg/kg
i. v.	:	rat, LD_{50}	=	ca. 120 mg/kg

Discussion: The data available are sufficient for an Initial Hazard Assessment. With respect to the use pattern of sodium dodecyl sulphate only the acute oral and acute dermal toxicity data are considered relevant. These data indicate that sodium dodecyl sulphate is not toxic, but has to be classified as harmful (labelling: "Xn").

3.1.2 Repeated dose toxicity

The following animal data were considered to establish the ***N***o ***O***bserved ***A***dverse ***E***ffects ***L***evel (NOAEL) and the ***L***owest ***O***bserved ***A***dverse ***E***ffects ***L***evel (LOAEL):

1. Sodium dodecyl sulphate (86% active material) was tested for sub-chronic toxicity in a 90-day feeding study in Carworth Farm 'E' strain rats. Groups of 12 male and 12 female animals were fed dietary levels of 40, 200, 1,000 or 5,000 ppm active material. The NOAEL- and LOAEL-values in mg kg^{-1} day^{-1} were calculated using the following parameters: 250 g rat body weight and 25 g diet consumed per day. Control groups of 18 male and 18 female rats received unsupplemented diet. Body weights and food intake were recorded weekly for all animals. The urine was analysed and terminal blood samples were taken. At autopsy, a gross pathological examination was carried out. It was found, that in the 5,000 ppm group the females had increased liver weights (4).

Result : NOAEL = 100 mg kg^{-1} day^{-1}
LOAEL = 500 mg kg^{-1} day^{-1}

2. Sodium dodecyl sulphate (of undefined quality) was tested for chronic toxicity in a two-year feeding study in Osborne-Mendel rats. Groups of 12 weaning males (21 days old) were fed dietary levels of 0.25%, 0.5% or 1% sodium dodecyl sulphate. A control group received a diet without test substance. The NOAEL-value in mg kg^{-1} day^{-1} was calculated using the following parameters: 250 g rat body weight and 25 g diet consumed per day. Body weights and food consumption were determined at weekly intervals. At termination of the experiment an autopsy with a gross examination of tissues was carried out. No differences were observed between sodium dodecyl sulphate-treated and control groups (4).

Result : NOAEL = 1,000 mg kg^{-1} day^{-1}
LOAEL = not determined

3. Sodium dodecyl sulphate (Duponol PC) was tested for chronic toxicity in a one-year feeding study in beagles. Groups of 2 male and 2 female dogs were fed dietary levels of 0.67 %, 1 % or 2 % material. A control group received unsupplemented diet. Body weights were measured weekly and food intake was recorded daily for all animals. Blood samples were taken prior to placing the dogs on test and at 1, 3, 6 and 12 months. At termination of the experiment gross pathological and microscopic examinations were carried out. The only substance-related effect observed was a decreased rate in body weight gain at the highest dose level (4). The NOAEL- and LOAEL-values in mg kg^{-1} day^{-1} were calculated using the following parameters: 15 kg body weight and 600 g diet consumed per day.

Result : NOAEL = 400 mg kg^{-1} day^{-1}
LOAEL = 800 mg kg^{-1} day^{-1}

4. Sodium dodecyl sulphate (90% active material) was tested for systemic toxicity in Sprague-Dawley rats in a 28-day study. The test was done according to GLP. The compound was administered 5 days/week for 4 consecutive weeks by gavage to 10 male and 10 female animals per dose. The experiment was started with doses of 0 (control), 30, 100 and 300 mg kg^{-1} body weight. Because no signs of toxicity were observed after two weeks, for the animals in group 4 the dose was increased to 600 mg kg^{-1} body weight. At termination of the experiment hematological

investigation and macroscopic/microscopic examination were carried out. Whereas in the low and middle dose group no treatment-related changes were observed, the following changes were recorded for the high dose group: decreased weight gain (males), increased relative weights of kidney, brain and liver, decrease of thymus weight, ulcerations and bleedings in the stomach, and reversible alterations of the tongue, myocard and forestomach. Further, significant increased levels of the enzyme alanine-aminotransferase (ALT) were found (21). In conjunction with the observed increase in liver weight this is judged to indicate the onset of hepatotoxicity.

Result : NOAEL = 100 mg kg^{-1} day^{-1}

LOAEL = 300/600 mg kg^{-1} day^{-1}

Discussion: The repeated dose toxicity of sodium dodecyl sulphate was studied extensively. Tests range from sub-acute (28 days) to chronic (2 years in rat) studies. Further, the substance was tested in two different species (rat and dog) and by means of two different routes of administration (diet and gavage). As can be seen, the results in the rat studies differed with strains and the route of application. As a trend, the substance was much better tolerated when administered in the diet. In the case of an administration by gavage relatively high local concentrations can result in the stomach and intestines whereas in the case of administration via the diet the test substance is ingested in several portions during the day; thus local concentrations stay low. Because the primary effect of sodium dodecyl sulphate is a local irritation of the gastro-intestinal tract, a bolus administration resulting in a high local substance concentration is toxicologically different from an administration by diet, although the doses administered are numerical the same. For the assessment of the health effects in humans (ingestion of toothpaste by children), the scenario of a repeated bolus administration is considered to be the most relevant.

Although the gavage study done on Sprague-Dawley rats is only a sub-acute study, it is considered to be the preferential one, because it gives detailed information on biochemical and histological parameters, it was done according to an EEC test protocol and GLP, and it used the most relevant route of administration. The representative NOAEL with respect to repeated dose toxicity is therefore:

$NOAEL_{rep.\ dose}$ = 100 mg $kg^{-1}day^{-1}$

This NOAEL-value is confirmed by the results of the sub-chronic and chronic studies which yielded the same or even higher NOAEL-values (up to 1,000 mg $kg^{-1}day^{-1}$).

3.1.3 Reproductive/Developmenal toxicity

3.1.3.1 Reproductive toxicity

Hemsworth (17) investigated the antifertility action of the substance in male Swiss albino mice. Ten animals were used per dose. The substance was administered by the oral route. The NOAEL-value in mg $kg^{-1}day^{-1}$ was calculated using the following parameters: 25 g mice body weight and 2.5 g diet consumed per day. Result: male mice fed diets containing 0.1 % for 6 weeks or 1.0 % for 2 weeks experienced no impairment of epididymal spermatozoa, although at the highest dose (1%) the animals suffered a significant reduction of average body weight. Keeping in mind that the $LOAEL_{rep.\ dose}$ for rats lies between 300 and 600 mg $kg^{-1}day^{-1}$, the observed reduction in body weight is probably caused by the systemic toxicity of the substance. The author stated that sodium

dodecyl sulphate has no adverse effect on fertility, even when administered at concentrations sufficient to cause a significant reduction in body weight (parental toxicity).

Result : $NOAEL_{reprod.}$ = 1,000 mg $kg^{-1}day^{-1}$

$LOAEL_{reprod.}$ = could not be established

Discussion: The study was not done according to a EEC- or OECD-protocol, neither to GLP. Nevertheless, the design of the study is considered appropriate, because doses up to significant parental toxicity were administered.

3.1.3.2 Developmental toxicity/Teratogenicity

1. CD-rats were exposed from day 6 to day 15 of gravidy to doses of 0, 0.2, 2.0, 300, and 600 mg $kg^{-1}day^{-1}$ sodium dodecyl sulphate by gavage. At doses of 300 and 600 mg $kg^{-1}day^{-1}$ slight to moderate maternal toxicity was observed. No effects on fetal morphogenesis were observed at 600 mg $kg^{-1}day^{-1}$ (4).

Result : $NOAEL_{develop.}$ = 600 mg $kg^{-1}day^{-1}$ (highest dose applied)

$LOAEL_{develop.}$ = could not be established

2. Mice (strain CD-1) were exposed from day 6 to day 15 of gravidy to doses of 0, 0.2, 2.0, 300, and 600 mg $kg^{-1}day^{-1}$ by gavage. At a dose of 300 mg $kg^{-1}day^{-1}$ slight to moderate, at a dose of 600 mg $kg^{-1}day^{-1}$ considerable maternal toxicity was observed. Total resorption and/or increased incidence of litter loss were found at the highest dose of 600 mg $kg^{-1}day^{-1}$. No effects on fetal morphogenesis were observed, even at 600 mg $kg^{-1}day^{-1}$ (4).

Result : $NOAEL_{develop.}$ = 300 mg $kg^{-1}day^{-1}$

$LOAEL_{develop.}$ = 600 mg $kg^{-1}day^{-1}$

3. New Zealand rabbits were exposed from day 6 to day 18 of gravidy to doses of 0, 0.2, 2.0, 300 and 600 mg $kg^{-1}day^{-1}$ by gavage. At a dose of 300 mg $kg^{-1}day^{-1}$ slight to moderate, at a dose of 600 mg $kg^{-1}day^{-1}$ considerable maternal toxicity was observed. Abortion, total resorption and/or increased incidence of litter loss were found at a dose of 600 mg $kg^{-1}day^{-1}$. No effects on fetal morphogenesis were observed, even at the highest dose (4).

Result : $NOAEL_{develop.}$ = 300 mg $kg^{-1}day^{-1}$

$LOAEL_{develop.}$ = 600 mg $kg^{-1}day^{-1}$

Discussion: Developmental toxicity/teratogenicity of sodium dodecyl sulphate was investigated in three different species. Although the studies were not conducted under GLP or in accordance to established EEC- or OECD-protocols, their design (doses that exert maternal toxicity are included) and their results are considered to be appropriate. Mice and rabbit are the most sensitive species, both exhibiting a NOAEL of 300 mg $kg^{-1}day^{-1}$ and a LOAEL of 600 mg $kg^{-1}day^{-1}$. Therefore, the representative NOAEL with respect to developmental toxicity/teratogenicity is:

$NOAEL_{develop.}$ = 300 mg $kg^{-1}day^{-1}$

3.1.4 Genetic toxicity

3.1.4.1 Bacterial Gene Mutation Tests

Test type	:	Ames test
Test system	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test substance	:	97 % sodium dodecyl sulphate (< 3% tetradecyl-)
Test concentration	:	5, 10, 20, 40, and 80 µg per plate (without S-9-mix) 2.5, 10, 40, 160, and 640 µg per plate (with S-9-mix)
Controls	:	positive = yes, negative = yes

Result = negative (4)

Remark: The substance was tested to be negative in three independent laboratories, with and without metabolic activation.

3.1.4.2 Mammalian Gene Mutation Tests

Test type	:	Mouse lymphoma cell forward mutation assay
Test system	:	Lymphoma cell culture tk^+/tk^- of L5178Y mice
Test substance	:	Sodium dodecyl sulphate from the US NTP chemical repository (quality not stated)
Metabolic activation	:	with and without
Exposure period	:	4 hours
Test concentration	:	10, 20, 30, 40, 50, 60, 70 µg per ml (without S-9) 10, 20, 30, 40, 50, 60, 70 µg per ml (with S-9)
Controls	:	positive = yes, negative = yes

Result = negative (18)

3.1.4.3 Mammalian Chromosome Mutation Test

Test type	:	Micronucleus assay
Test system	:	Rat bone marrow cells exposed in vivo
Test substance	:	Sodium dodecyl sulphate 99% purity from BDH
Route of admin.	:	oral feed
Exposure period	:	90 days
Doses	:	0.0, 0.56, and 1.13% in diet
Controls	:	positive = yes, negative = yes

Result = negative (20)

Test type	:	Sister chromatid exchange assay
Test system	:	Chinese hamster ovary cells exposed in vitro
Test substance	:	Sodium dodecyl sulphate, purity not stated
Doses	:	0 - 160 ug/ml
Metabolic activation	:	with and without

Controls : positive = yes, negative = yes

Result = negative (4)

Remark: The dose of 160 ug/ml was stated to be toxic. A further SCE assay was reported from another laboratory, using much higher doses. In a first trial with doses up to 500 ug/ml a negative result was found. In a second trial using doses from 500 - 800 ug/ml a weak positive result was reported. Both test series were spoiled by precipitations and the toxic effects of the substance, and no data with respect to the substance tested were given. The latter assay was therefore not considered for the hazard assessment.

Discussion: Sodium dodecyl sulphate was extensively tested for genetic toxicity. Neither the bacterial tests nor the various tests in mammalian systems (in vitro and in vivo) have shown any indication of genotoxicity. Based on the proposed OECD action-scheme (19) there is "No need for follow-up tests" with respect to genetic toxicity.

3.2 Ecotoxicity

3.2.1 Aquatic organisms

A multitude of test results with aquatic organisms are available. Only the lowest effect concentrations to different organisms are related here. Test results whose validity could not be established, have been left out.

3.2.1.1 Toxicity to fish

Acute effect concentrations (96h-LC50) range from 1.48 to 30 mg/l. The most sensitive species are:

Menidia beryllina (several tests)	96h-LC50	1.48 -2.8 mg/l	(salt water sp.)
Atherinops affinis	96h-LC50	1.88 mg/l	(salt water sp.)
Macrones vittatus	96h-LC50	1.39 mg/l	(fresh water sp.)

Results from prolonged and long-term toxicity tests are also available:

Menidia beryllina (larvae)	7d-LC50	1.8 mg/l	(salt water sp.)
Cyprinodon variegatus (larvae)	7d-LC50	2.9 mg/l	(salt water sp.)
Pimephales promelas	8d-LC50	4.8 mg/l	(fresh water sp.)
(embryo-larval-test)	8d-NOEC	2.2 mg/l	
Salmo gairdneri	10d-LC50	2.85 mg/l	(fresh water sp.)
Saccobranchus fossilis (effect: visible symptoms, adult fish)	60d-NOEC	>= 2.24 mg/l	(fresh water sp.)

From the above data it becomes clear that the exposure duration has practically no influence upon the test results. The 8d-NOEC with *Pimephales promelas* may therefore beconsidered to be sufficient to cover the long-term toxicity endpoint. This is supported by the 60d-NOEC with adult fish (*Saccobranchus fossilis*).

3.2.1.2 Toxicity to invertebrates

Acute effect concentrations (EC50 values range from 0.72 to 108 mg/l). The most sensitive species are:

Daphnia magna	48h-EC50	1.8 mg/l	(fresh water sp.)
Artemia salina	96h-EC50	1.48 mg/l	(salt water sp.)
Acanthomysis sculpta	72h-EC50	0.95 mg/l	(salt water sp.)
Homarus americanus	96h-EC50	0.72 mg/l	(salt water sp.)
Crassostrea gigas	48h-EC50	0.84 mg/l	(salt water sp.)
Brachionus rubens	24h-LC50	1.35 mg/l	(fresh water sp.)
Brachionus calyciflorus	24h-LC50	1.4 mg/l	(fresh water sp.)
Limnaea peregra (effect: weight of shells)	6d-LOEC	0.606 mg/l	(fresh water sp.)

Results from long-term toxicity tests are also available:

Daphnia magna (effect: survival of parental organisms, reproduction rate)	40d-NOEC	2 mg/l	(fresh water sp.)
Ceriodaphnia dubia (effect: survival of parental organisms, reproduction rate)	5-7d-NOEC	6.48 - 10.8 mg/l	(fresh water sp.)
Hydra attenuata (effect: budding rate)	21d-NOEC	5.8 mg/l	(fresh water sp.)
Corbicula fluminea (effect: respiration inhibition)	30d-NOEC	0.65 mg/l	(fresh water sp.)

As with fish, the toxicity is practically independant of the exposure duration.

3.2.1.3 Toxicity to algae (lowest effect concentrations only)

The lowest recorded effect data is:

Scenedesmus quadricauda (effect: growth inhibition (biomass); TT = toxicity threshold, 3% effect)	8d-TT	0.02 mg/l	(fresh water sp.)

The species used was later identified as being *Scenedesmus subspicatus* (32); furthermore the toxicity threshold was fixed at 3% in this study; it is not clear, whether at the next higher concentrations, statistically significant effects occured. The same algae was recently tested according to a standard guideline by the same institute as well as by the producer, with the following results:

Scenedesmus subspicatus (effect: growth inhibition (biomass & growth rate))	72h-NOEC	30 mg/l	(fresh water sp.)
Scenedesmus subspicatus (effect: growth inhibition (biomass))	96h-EC20	15 mg/l	(fresh water sp.)

The older result of 8d-TT = 0.02 mg/l will therefore not be used for the risk assessment. Other test results are:

Selenastrum capricornutum 8d-EC50 3.75 mg/l (fresh water sp.)
(effect: growth inhibition (biomass))

Selenastrum capricornutum 4d-EC50 117 mg/l (fresh water sp.)
(effect: growth inhibition (biomass)) 4d-EC10 12 mg/l

Pseudoisochrysis paradoxa 2h-EC50 1.27 mg/l (salt water sp.)
(effect: incorporation of NaHCO3 and chlorophyll a content)

Champia parvula 48h-EC50 0.3 mg/l (salt water sp.)
(effect: development of cystocarps; 48h exposure followed by 5 - 7 d incubation without toxicant)

3.2.1.4 Toxicity to microorganisms

Many results on acute toxicity with *Photobacterium phosphoreum* are available: EC50 0.38 - 39 mg/l (5 - 30 min). Furthermore:

Uronema parduczi 20h-NOEC 0.75 mg/l

Pseudomonas putida 16h-TT 290 mg/l
(effect: growth inhibition (biomass); TT = toxicity threshold)

activated sludge (several tests) 3h-EC50 130-635 mg/l
(effect: respiration inhibition)

activated sludge 4h-EC50 24 mg/l
(effect: inhibition of nitrification)

3.2.2 Terrestrial organisms

3.2.2.1 Toxicity to plants

Cicer arietinum 48h-EC50 361 mg/l
Lupinus albus 48h-EC50 384 mg/l
(effect: reduction of primary root length of seedlings)

3.2.2.2 Toxicity to invertebrates

No data on toxicity to invertebrates are available

4. INITIAL ASSESSMENT

4.1. Consumer Exposure Risk Assessment

The exposure assessment has shown, that for consumers the primary route of exposure is oral ingestion by means of dentifrice, especially for children. Dermal absorption, inhalation, and oral intake through contaminated food and drinking water are of less importance. Nevertheless, the combined values of all relevant exposure paths are considered as the basis for the hazard assessment. The calculation of the safety margin is done with respect to the most sensitive population sub-group (children):

$$\frac{\mathbf{NOAEL}_{\textit{rep. dose}}}{\mathbf{EHE}_{\textit{consum, child}}} = \textbf{Safety margin for consumer hazard}$$

$$\frac{\mathbf{100\ mg\ kg^{-1}day^{-1}}}{\mathbf{0.158\ mg\ kg^{-1}day^{-1}}} = \mathbf{> 600}$$

Discussion of the safety margin for consumer hazard assessment:

It was shown that for sodium dodecyl sulphate repeated dose toxicity is the most sensitive health effects parameter. Indications of developmental toxicity/teratogenicity (ambiguous results) were observed only at much higher doses which are accompanied by considerable maternal toxicity. No indication for reproductive toxicity (by means of male fertility) of the substance was found (a LOAEL could not be established). The corresponding NOAEL-values are 300 mg $kg^{-1}day^{-1}$ for developmental toxicity/terato-genicity and 1,000 mg $kg^{-1}day^{-1}$ for reproductive toxicity, respectively. Therefore, the $NOAEL_{\textit{rep. dose}}$ is the "most sensitive value", and is to be used for the hazard assessment.

The systemic toxicity of sodium dodecyl sulphate was studied extensively. Tests conducted range from sub-acute (28 days) to chronic (2 years in rat) studies. Further, the substance was tested in two different species (rat and dog) and by means of two different routes of administration (diet and gavage). From the exposure assessment (dentifrices scenario) administration by gavage seems to reflect best the toxicological situation that the most exposed sub-group (children) is faced with.

The 28-days gavage study with Sprague-Dawley rats is considered to be the preferential one to establish the "most sensitive" NOAEL-value because it meets high quality standards, except that it is only a sub-acute study (see below). It was done according to an established EEC test protocol, it is a GLP study, and it gives detailed information about biochemical, hematological, histological and macroscopical findings. A sufficient number of animals was used per dose group and both sexes were included in the test. The dose range investigated was adequate (half-log scale), and NOAEL- and LOAEL-values were determined. A clear dose-response relationship was established. The doses of 30 mg $kg^{-1}day^{-1}$ and 100 mg $kg^{-1}day^{-1}$ were tolerated without any signs of toxicity and weight gains of the animals were normal. The only difference between the control group and the 100 mg $kg^{-1}day^{-1}$ dosed animals was that the latter had some white precipitation in the stomach and upper intestines. This, however, was not considered to be an adverse effect. On the other hand, the animals

in the highest dose group (300/600 mg $kg^{-1}day^{-1}$) showed marked signs of toxicity, and two animals of this group died. Food consumption and weight gains were reduced in male animals. Water consumption was increased. The number of leucocytes was increased. Significant increased levels of the enzyme alanine-aminotransferase (ALT) were found which in conjunction with the observed increase in liver weights may be indicative for hepatotoxicity. Macroscopical examination of the inner organs, however, did not reveal alterations in comparison to the controls, except for the tongue, myocard and forestomach. In addition, ulcerations and bleedings were found in the stomach. Damage of the tongue and myocard were completely reversible within 30 days, whereas the damage of the forestomach mucosa was only in part reversible.

Taking together all observed biochemical, hematological, histological and macroscopical findings, it can be stated that the $LOAEL_{rep.\ dose}$ is defined primarily by the irritating effect of the substance to the pharynx and stomach. The effects observed on the liver probably result from the continuing inflammation induced by the substance. Although these effects are considered to indicate the onset of systemic toxicity, they are not judged to be severe effects. In other words, the NOAEL-value established in this study is on the ”safe side”. This conclusion is supported by the results of the sub-chronic and chronic animal studies and by human experience. The human experience originated from experimenal data on ulcer treatment using alkyl sulphates that were generated in the 40’s and 50’s. It is reported that 1 g sodium alkyl sulphate per day taken for 8 weeks was without toxic effect (22). In another study patients received up to 5.5 g of sodium hexadecyl sulphate per day for 20 days without toxic effects (23). This corresponds to a dose of about 80 mg kg^{-1} day^{-1}.

Children in general are exposed to higher concentrations of sodium dodecyl sulphate than adults by the oral route, because their intake is only marginally lower or even higher (dentifrice), but their body-size is significantly smaller. A unique situation may exist for bottle-fed babies, which are brought up with contaminated milk powder. All in all, the exposure assessment shows, that the most sensitive consumer sub-group are the children.

The safety margin for consumer hazard assessment was calculated for the most exposed consumer sub-group using the ”most sensitive” health effects parameter. Taking further into account the quality and quantity of data, ***the established safety margin of > 600 is judged to be more than sufficient to conclude that sodium dodecyl sulphate is of no concern for consumers.***

4.2 Occupational hazard assessment

As far as workers are concerned the exposure assessment has shown that the relevant routes of exposure at the workplace are inhalation of the substance and absorption through exposed skin. Oral intake is of negligible importance and is not considered for the hazard assessment. The calculation of the safety margin for occupational exposure is:

$$\frac{\mathbf{NOAEL_{rep.\ dose}}}{\mathbf{EHE_{occupational}}} = \textbf{Safety margin for occupational hazard}$$

$$\frac{\mathbf{100\ mg\ kg^{-1}day^{-1}}}{\mathbf{0.100\ mg\ kg^{-1}day^{-1}}} = \mathbf{1{,}000}$$

Discussion of the safety margin for occupational hazard assessment:

From the assessment of the human health effects it is known that for sodium dodecyl sulphate repeated dose toxicity is the most sensitive parameter. Therefore, the $NOAEL_{rep.\ dose}$ of 100 mg $kg^{-1}day^{-1}$ is adequate for the calculation of the safety margin. One weak point, however, that has to be taken into account for the judgement of the safety margin is that the $NOAEL_{rep.\ dose}$ was established for the oral route and not for inhalation or topical application which are the primary routes of exposure at the workplace. ***However, the established safety margin of 1,000 is judged to be sufficient to conclude that sodium dodecyl sulphate is of no concern at the workplace.***

4.3 Hazard assessment for combined consumer and occupational exposure

For workers, not only the occupational exposure is relevant, but the combined consumer and occupational exposure, because exposure to sodium dodecyl sulphate from the use of consumer products and the exposure at the workplace may add up. The calculation of the safety margin for combined consumer and occupational exposure for workers is:

$$\frac{\mathbf{NOAEL}_{rep.\ dose}}{\mathbf{EHE}_{worker,\ total}} = \textbf{Safety margin for hazard for workers}$$

$$\frac{\mathbf{100\ mg\ kg^{-1}day^{-1}}}{\mathbf{0.126\ mg\ kg^{-1}day^{-1}}} = \textbf{ca. 800}$$

Discussion of the safety margin for the hazard assessment of workers:

From the assessment of the human health effects it is known that repeated dose toxicity is the most sensitive parameter. Therefore, the $NOAEL_{rep.\ dose}$ is adequate for the calculation of the safety margin (for a more detailed discussion see chapter 4.1). The NOAEL given is appropriate without any reservations only for the fraction that consumer products contribute to the total exposure, i.e. for 1/3. For the judgement of the occupational safety margin it has to be taken into account that the NOAEL given was established for the oral route and not for inhalation or topical application of the substance which are the primary routes of exposure at the workplace. On the other hand it has to be taken into account that the total Estimated Human Exposure calculated above is considered to be a worst case scenario. It assumes that the workers are not protected by masks and gloves. Under normal circumstances, however, the workers are protected. This would reduce the total occupational exposure by at least an order of magnitude. ***Therefore, the established safety margin of ca. 800 is judged to be sufficient to conclude that sodium dodecyl sulphate is of no concern for workers.***

4.4 Assessment of environmental hazards

4.4.1 Aquatic compartment

The aquatic effect concentrations are very heterogeneous. For fish and invertebrates, the effect concentrations determined in tests on acute toxicity are of the same order as those recorded in tests on

prolonged toxicity. On the whole, salt water species seem to be somewhat more sensitive than fresh water species.

The lowest acute effect concentrations were determined with the alga *Champia parvula* (48h-EC50 = 0.3 mg/l) for salt water organisms and with the invertebrate *Brachionus rubens* (24h-LC50 = 1.35 mg/l) for fresh water species.

In long-term tests the lowest NOEC was determined with the clam *Corbicula fluminea* (30d-NOEC = 0.65 mg/l).

The assessment is performed based on acute effect data and on long-term effect data.

- assessment with acute effect data

According to the EU-Technical Guidance Document for the risk assessment of existing substances (25), the value of the safety factor would normally be 1000. But due to the availability of data from a wide selection of species covering additional taxonomic groups, a safety factor of **100** seems to be most appropriate.
Based on the guidance document for the initial assessment of aquatic effects proposed by the OECD, a safety factor of **F = 100** has also to be chosen.
With the lowest acute aquatic effect concentration with a fresh water species of 1.35 mg/l:

$$\textbf{PNEC} = \frac{1350}{100} = \textbf{13.5 µg/l}$$

$$\textbf{PEC/PNEC} = \frac{4.6}{13.5} = \textbf{0.34}$$

A comparison of a local PEC with a PNEC based on salt water species is not justified. A comparison with a regional PEC is preferable as a higher dilution as well as biodegradation in inland surface waters are considered in the regional PEC. Based on the lowest acute aquatic effect concentration with a salt water species of 0.3 mg/l, the PNEC would be 3 µg/l. With a regional environmental concentration of 2.3 µg/l :

$$\textbf{PEC/PNEC} = \frac{PEC_{regional}}{PNEC} = \frac{2.3}{3} = \textbf{0.77}$$

As in both cases PEC/PNEC < 1, there is at present no risk to the aquatic compartment.

- assessment with long-term effect data

According to the EU-Technical Guidance Document for the risk assessment of existing substances (25), the value of the safety factor would be **10**.
Based on the guidance document for the initial assessment of aquatic effects proposed by the OECD, a safety factor of **F = 10** has also to be chosen.

With the lowest long-term NOEC with aquatic species of 0.65 mg/l:

$$\textbf{PNEC} = \frac{650}{10} = \textbf{65 µg/l}$$

$$\textbf{PEC/PNEC} = \frac{4.6}{65} = \textbf{0.07}$$

As PEC/PNEC < 1, there is at present no risk to the aquatic compartment.

4.4.2 Terrestrial compartment

For the soil compartment, only an indicative risk assessment can be performed, as only tests with plants have been performed. With an assessment factor of 1000, a PNEC of 361 µg/l can be determined (based on the lowest acute effect concentration of 361 mg/l (48h-EC50)). The highest calculated concentration of 30 µg/l pore water is chosen as PEC.

$$\textbf{PEC/PNEC} = \frac{30}{361} = \textbf{0,08}$$

Although tests for less than 3 trophic levels are available, the above calculated PEC/PNEC-ratio does not indicate a risk for the soil compartment.

5. CONCLUSIONS AND RECOMMENDATIONS

Conclusion

The environmental risk assessment shows that for the hydrosphere as well as the soil compartment, there is at present no risk to the environment from SDS to be expected, as all PEC/PNEC values are lower than 1.
The human health hazard assessment for sodium dodecyl sulphate shows that at present the substance is of no concern for the general public (consumers) and for workers.

Recommendations

There is at present no need for further work.

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S I D S

D o s s i e r

Existing Chemical	ID: 151-21-3
CAS No.	151-21-3
EINECS Name	sodium dodecyl sulphate
EC No.	205-788-1
TSCA Name	Sulfuric acid monododecyl ester sodium salt
Molecular Formula	C12H26O4S.Na

Producer Related Part	
Company:	Henkel KGaA
Creation date:	05-OCT-1992
Substance Related Part	
Company:	Henkel KGaA
Creation date:	05-OCT-1992
Memo:	Basis for OECD Risk Assessment (Status 30-MAY-95)

Printing date:	28-JAN-2003
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Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

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Remark: The dataset was prepared by Henkel KGaA (D) in the names of the following co-producers:

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1.0.2 Location of Production Site, Importer or Formulator
-

1.0.3 Identity of Recipients
-

1.0.4 Details on Category/Template
-

1.1.0 Substance Identification
-

1.1.1 General Substance Information

Substance type: organic
Physical status: solid
Purity: >= 85 - % w/w

Remark: 1. The dataset was prepared by Henkel KGaA (D) in the names of the following co-producers:

1. Aarhus Oliefabrik A/S (DK)

2. Sidobre Sinnova (F)

2. Solid product is commercially available as powder, needles or granulate. Also commercially available as aqueous pastes of ca. 30 - 65% active substance. If not otherwise stated the data given refer to the solid substance with > 85% active material.

1.1.2 Spectra
-

1.2 Synonyms and Tradenames

Akyposal NLS

Alsocoap LN-40,LN-90

Arsul WAQ

Avirol SL-2010

Calfoam SLS-30

Carsonol SLS

Cedepon LS-30PM

DeSonol S

dodecyl alcohol, hydrogen sulfate, sodium salt

dodecyl sulfate, sodium salt

Dodecylsulfat, Na-Salz

Drewpon 100

Duponol C

Elfan 200

Empicol 0045

Empimin LR28

Equex S

Gardinol WA Paste

lauryl sulfate, sodium salt

Laurylsulfat, Na-Salz

Laurylsulfat, Natriumsalz

Lonzol LS-300

Manro DL28

Marlinat DFK30

Montovol RF-10

n-Dodecylhydrogensulfat, Natriumsalz

Natriumdodecylsulfat

Natriumlaurylsulfat

NCI-C50191

Neopon LS/NF

Nikkol SLS

Norfox SLS

Nutrapon DL 3891

Polystep B-3

Rewopol 15/L

Rewopol NLS

Sactol 2S3

Sandoz Sulfate WA Dry

SCHWEFELSAEURE, MONODODECYL-ESTER, NATRIUM-SALZ

Schwefelsäure, mono-Dodecyl-Ester, Na-Salz

SDS

Serdet DFK 40

Sermul EA150

Sipon 21LS

Sodium Dodecyl Sulfate

sodium dodecyl sulphate

Sodium Lauryl Sulfate

Sodium lauryl sulfate (INCI)

sodium lauryl sulphate

Sodium lauryl sulphate

Standapol WA-AC

Stepanol ME Dry

Sulfetal C38

Sulfochem SAC,SLC,SLS

Sulfopon 102

Sulfotex LCX

Sulfuric acid monododecyl ester sodium salt

Sulfuric acid, mono dodecyl ester sodium salt

sulfuric acid, monododecyl ester, sodium salt

Sulphonated Lorol Paste

Swascol 1P

Texapon K 12

Texapon K-12 Granules

Ultra Sulfate SL-1

Ungerol LS,LSN

Unipol WA-AC

Zoharpon LAS

1.3 Impurities

CAS-No: 7732-18-5
EC-No: 231-791-2
EINECS-Name: water, distilled, conductivity or of similar purity
Contents: <= 7.5 - % w/w

CAS-No: 7757-82-6
EC-No: 231-820-9
EINECS-Name: sodium sulphate
Contents: <= 6.5 - % w/w

CAS-No: 91648-54-3
EC-No: 293-916-7
EINECS-Name: Sulfuric acid, mono-C14-16-alkyl esters, sodium salts
Contents: ca. 2 - 10 % w/w

Remark: The main impurity is the C14 compound.

CAS-No: 7647-14-5
EC-No: 231-598-3
EINECS-Name: sodium chloride
Contents: <= 1.5 - % w/w

EINECS-Name: unsulfated material
Contents: <= 1 - % w/w

CAS-No: 85338-42-7
EC-No: 286-718-7
EINECS-Name: Sulfuric acid, mono-C8-10-alkyl esters, sodium salts
Contents: ca. 0 - 4 % w/w

1.4 Additives

Remark: None

1.5 Total Quantity

Quantity: 1000 - 5000 tonnes produced in 1990

Quantity: 1000 - 5000 tonnes produced in 1991

Quantity: 1000 - 5000 tonnes produced in 1992

Quantity: 5000 - 10000 tonnes produced in 1993

Remark: Production in 1993 was only slightly above the lower border of 5.000 t/year.

1.6.1 Labelling

Labelling: no labelling required (no dangerous properties)

Remark: Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)
No labelling because active substance 15% only

Labelling: provisionally by manufacturer/importer
Symbols: (Xn) harmful
R-Phrases: (22) Harmful if swallowed
(38) Irritating to skin
(41) Risk of serious damage to eyes
S-Phrases: (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of...
(37/39) Wear suitable gloves and eye/face protection
(46) If swallowed, seek medical advice immediately and show this container or label

Remark: AIDA-Grunddatensatz, (LIT 3981)
Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)
Labelling for sodium dodecylsulphate > 50 % active substance in all physical forms that do not dust, i.e. granules, pastes, etc.

Labelling: provisionally by manufacturer/importer
Symbols: (Xn) harmful
R-Phrases: (20/22) Harmful by inhalation and if swallowed
(37/38) Irritating to respiratory system and skin
(41) Risk of serious damage to eyes
S-Phrases: (22) Do not breathe dust
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of ...
(37/39) Wear suitable gloves and eye/face protection
(46) If swallowed, seek medical advice immediately and show this container or label

Remark: AIDA-Grunddatensatz, (LIT 3981)
BIAS 93 0997/1

Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)
Labelling for sodium dodecylsulphate > 85 % active substance in physical forms that may lead to dust formation, i.e. needles and powders.

Labelling: provisionally by manufacturer/importer
Symbols: (Xi) irritating
R-Phrases: (38) Irritating to skin
(41) Risk of serious damage to eyes
S-Phrases: (26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(28) After contact with skin, wash immediately with plenty of ...
(37/39) Wear suitable gloves and eye/face protection

Remark: BIAS 93 0997/1
Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)

1.6.2 Classification

Classified: no classification required (no dangerous properties)

Remark: Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)
No labelling because active substance 15% only

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (22) Harmful if swallowed
(38) Irritating to skin
(41) Risk of serious damage to eyes

Remark: AIDA-Grunddatensatz, (LIT 3981)
Classification for sodium dodecylsulphate > 50 % active substance in all physical forms that do not dust, i.e. granules, pastes, etc.
Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)

Classified: provisionally by manufacturer/importer
Class of danger: harmful
R-Phrases: (20/22) Harmful by inhalation and if swallowed
(37/38) Irritating to respiratory system and skin
(41) Risk of serious damage to eyes

Remark: BIAS 93 00997/1
Classification for sodium dodecylsulphate > 85 % active substance in physical forms that may lead to dust formation, i.e. needles and powders.
Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)

Classified: provisionally by manufacturer/importer
Class of danger: irritating
R-Phrases: (38) Irritating to skin
(41) Risk of serious damage to eyes

Remark: BIAS 93 0997/1
Information: TTB-Gesetzliche Regelungen, (LIT 8000/375)

1.6.3 Packaging
-

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Type: industrial
Category: Personal and domestic use

Type: industrial
Category: Polymers industry

Type: industrial
Category: Public domain

Type: industrial
Category: other: fire extinguisher factories

Type: use
Category: Cleaning/washing agents and disinfectants

Type: use
Category: Cosmetics

Type: use
Category: Flame retardants and fire preventing agents

Type: use
Category: Surface-active agents

Type: use
Category: Surface-active agents

Type: use
Category: other: emulsifier in the plastics industry

1.7.1 Detailed Use Pattern
-

1.7.2 Methods of Manufacture
-

1.8 Regulatory Measures
-

1.8.1 Occupational Exposure Limit Values
-

1.8.2 Acceptable Residues Levels
-

1.8.3 Water Pollution

Classified by: KBwS (DE)
Labelled by: KBwS (DE)

Class of danger: 2 (water polluting)

Remark: According to the German regulation "Wassergefaehrdungsklassen"
Reliability: (1) valid without restriction

1.8.4 Major Accident Hazards

Substance listed: no

1.8.5 Air Pollution
-

1.8.6 Listings e.g. Chemical Inventories
-

1.9.1 Degradation/Transformation Products
-

1.9.2 Components
-

1.10 Source of Exposure
-

1.11 Additional Remarks

Remark: Dossier, in:
Henkel KGaA, unpublished data, Archive-No. TBD 900619

1.12 Last Literature Search
-

1.13 Reviews
-

2.1 Melting Point

Value: 204 - 207 degree C

Method: other

Remark: no information about method used.
(161)

2.2 Boiling Point
-

2.3 Density

Type: bulk density
Value: 200 - 300

Method: other: DGF-H-II-1b

Remark: data for powder
(70)

Type: bulk density
Value: 400 - 600 kg/m3

Method: other: DGF-H-II-1b

Remark: data for needles
(72)

Type: bulk density
Value: 450 - 600 kg/m3

Method: other: DGF-H-II-1b

Remark: data for granulate
(71)

2.3.1 Granulometry
-

2.4 Vapour Pressure
-

2.5 Partition Coefficient

log Pow: 1.6

Remark: no information about method used.
(161)

log Pow: = 1.6

Method: other (measured): W.R. Glave & C. Hansch, unpublished analysis; cited in: A. Leo et al., Chemical Reviews 71 (1971),

525-616
GLP: no data

Test condition: pH 5.4
Test substance: Dodecyl Sulfate, Sodium Salt; no further information
(4)

2.6.1 Solubility in different media

Value: ca. 150 g/l at 20 degree C
pH value: 6 - 9
Conc.: 10 g/l at 20 degree C
(46) (70) (71) (72)

2.6.2 Surface Tension
-

2.7 Flash Point
-

2.8 Auto Flammability
-

2.9 Flammability
-

2.10 Explosive Properties
-

2.11 Oxidizing Properties
-

2.12 Dissociation Constant
-

2.13 Viscosity
-

2.14 Additional Remarks
-

3.1.1 Photodegradation
-

3.1.2 Stability in Water
-

3.1.3 Stability in Soil

Type: laboratory
Radiolabel: no
Soil temperature: 25 degree C
Soil classification: other: Clay loam, humus 11.0 %
Content of clay: 22.5 %
Organ. carbon: 6.4 %
pH: 6.7
Cation exch. capac.: 55.4 meq/100 g soil dry weight
Dissipation time
Dissipation: ca. 100 % after

Method: other: soil perfusion method, i.e. circulation of SDS-solution through a soil column
Year: 1987
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Concentration of test substance in perfusion fluid was 50 mg/l.
Dissipation relative to adsorption and biodegradation (primary degr.).Determination of disappearance through ferroin reagent active subtances; repeated perfusions through the same column did not give any sign of substance retention.
Dissipation was ca. 100% after 6-7 days.
(5)

3.2.1 Monitoring Data (Environment)
-

3.2.2 Field Studies
-

3.3.1 Transport between Environmental Compartments

Type: adsorption
Media: other: water - activated carbon
Method: other: determination of adsorption isotherms

Result: Langmuir adsorption capacity of activated carbon (particle size range: 500-710 um) for SDS: 361 mg/g.
Test condition: Adsorbent: activated carbon (Filtrasorb 400) milled and sieved into various particle sizes.
Adsorption isotherms were determined in distilled water at 27 degr. C by shaking a fixed weight of carbon with SDS solutions of known initial concentration. Analysis of SDS concentration by determination of TOC (Total Organic Carbon).
(113)

Type: adsorption
Media: water - soil
Method: other: determination of adsorption isotherms

Result: SDS showed a fast adsorption phase of < 20 min.
Henry`s law adsorption constants for 2 separate batches of sediment:
Sediment S1: 70.2 +- 9.2 dm3/kg
Sediment S2: 99.1 +- 12.3 dm3/kg
Test condition: Adsorbent: sediment obtained from artificial pond; dried to constant weight and succesively passed through sieves down to 0.125 mm size. Mineral composition: mainly quartz and calcite, some feldspars and mica present.
Adsorption isotherms were determined at 25 degr. C in 0.01 M NaHCO3 at pH 7.6. Time allowed for equilibrium: 20 min.
Analysis of SDS concentration by Methylene Blue Assay (spectrophotometric assay of Methylene Blue complex at 650 nm). Organic carbon content, 22.2% (w/w).
(109)

Type: adsorption
Media: water - soil
Method: other: see Test Condition
Year: 1989

Result: % elimination:

lime + FeSO4	lime + FeCl3
5.6%	3.1%

Test condition: Adsorption of SDS on lime (CaO) in combination with a flocculant/precipitant (FeSO4 or FeCl3) was studied:
SDS (30 mg/l) was reacted with a mixture of lime (300 mg/l) and FeSO4 (400 mg/l) or FeCl3 (conc. not given) for 15 min, allowed to settle for further 10 min, filtered and the filtrate analysed for MBAS.
(137)

3.3.2 Distribution
-

3.4 Mode of Degradation in Actual Use
-

3.5 Biodegradation

Type: aerobic
Inoculum: domestic sewage
Concentration: 2 mg/l related to Test substance
Degradation: ca. 85 % after 30 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1975
GLP: no data

Remark: Parameter: %BOD/BOD theoretical. 99% MBAS removal.
(58) (64)

Type: aerobic
Inoculum: domestic sewage
Concentration: 2 mg/l related to Test substance
Degradation: 93 % after 30 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year: 1986
GLP: no data

Remark: Parameter: %BOD/COD. 99% MBAS removal.
With inocula from different soil suspensions comparable results were obtained (90 - 94%).
(133)

Type: aerobic
Inoculum: other: no information
Degradation: ca. 100 % after 8 day(s)
Result: readily biodegradable

Method: OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"

Remark: No particulars on method mentioned. Data evaluated from graph.
(136)

Type: aerobic
Inoculum: activated sludge
Concentration: 250 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 97 % after 14 day(s)
Result: inherently biodegradable

Method: OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year: 1979
GLP: no data

Remark: Parameter: % DOC removal
(64)

Type: aerobic
Inoculum: other: self-inoculation
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)

Method: OECD Guide-line 303 A "Simulation Test - Aerobic Sewage Treatment: Coupled Unit Test"
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Rate of degradation: 107 +- 6 % (95% confidence limits).

At 100 mg/l influent concentration removal was 96 +- 1.5 % Retention time: 3 h; no working-in time; parameter: % COD removal.

(58) (64)

Type: aerobic
Inoculum: activated sludge
Concentration: 40 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 100 % after 28 day(s)
Result: readily biodegradable

Method: other: AFNOR T 90.302 (1977), parameter: %DOC removal.
Year: 1979
GLP: no data

(64)

Type: aerobic
Inoculum: domestic sewage
Concentration: 20 mg/l related to Test substance
Degradation: ca. 95 % after 1 day(s)

Method: other: Column with glass beads, mineral medium, parameter: %MBAS removal
Year: 1973
GLP: no data

Remark: Data evaluated from graph.

(11)

Type: aerobic
Inoculum: activated sludge
Concentration: 20 mg/l related to Test substance
Degradation: 99.5 % after 20 day(s)

Method: other: Decree Concerning the Degradation of Anionic and Nonionic Surfactants in Detergents and Cleansing Agents, Part 2 Confirmatory Test; Bundesgesetzblatt, 1977, Part I, January 30, 1977 (DIN 38412 Teil 24).
Year: 1971
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Concentration related to MBAS. Parameter: % MBAS removal (99% TOC removal).
No significant changes in the results with influent concentrations of 50, 100 and 200 mg/l.

(91)

Type: aerobic
Inoculum: domestic sewage
Concentration: 20 mg/l related to Test substance
Degradation: 99 %

Method: other: Decree Concerning the Degradation of Anionic and Nonionic Surfactants in Detergents and Cleansing Agents, Part 2 Confirmatory Test; Bundesgesetzblatt, 1977, Part I, January 30, 1977 (DIN 38412 Teil 24).
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Concentration related to MBAS. Parameter: % MBAS removal.
(58)

Type: aerobic
Inoculum: domestic sewage
Concentration: 5 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: > 100 % after 19 day(s)
Result: readily biodegradable

Method: other: Modifizierter OECD Screening Test, OECD Guideline 301 E adopted 12 May 81, EG-Richtlinie 84/449/EWG, Teil C.3 im EG-Amtsblatt L 251, ISO 7824 (1984), draft
Year: 1979
GLP: no data

Remark: Degradation rate was 107% after 19d. Parameter: %DOC removal
(64)

Type: aerobic
Inoculum: domestic sewage
Concentration: 5 mg/l
Degradation: 99 % after 19 day(s)

Method: other: OECD Screening Test according to "Verordnung ueber die Abbaubarkeit anionischer und nichtionischer grenzflaechenaktiver Stoffe in Wasch- und Reinigungsmitteln vom 30.1.1977". Bundesgesetzblatt Teil I, S. 244.
Year: 1975
GLP: no data

Remark: Concentration related to MBAS. Parameter: % MBAS removal.
(58)

Type: aerobic
Inoculum: other: diverse sources (surface waters, sewage plant effluents)
Concentration: 100 mg/l related to Test substance
Degradation: 93 % after 14 day(s)
Result: readily biodegradable

Method: other: ORIGINAL-MITI-Test, Biodegradability and Bioaccumulation Test of Chemical Substances (C-5/98/JAP) 1978
Year: 1979
GLP: no data
Remark: Parameter: % DOC removal. 70% BOD/BOD theoretical using Sapromat.
(64)

Type: aerobic
Inoculum: activated sludge, adapted
Concentration: 75 mg/l related to Test substance
Degradation: 97.9 % after 25 day(s)

Method: other: Pitter-test; mineral medium, parameter: %BOD/COD at 25 degr. C (99.5% MBAS removal after 20 d).
Year: 1963
GLP: no data
Test substance: other TS: SDS, purity ca. 100%

Remark: 14 d adaptation.
(128)

Type: aerobic
Inoculum: other: river water

Method: other: River Water Die Away Test
Year: 1985
GLP: no data
Test substance: other TS: no further data

Remark: The degradation of sodium dodecyl sulfate as a function of temperature was studied in water collected from Tama River, Japan:

100% degradation after
27 degr. C < 1 day
21 degr. C < 1 day data extracted from graph
15 degr. C ca. 1 day
10 degr. C ca. 3 days
(97)

Type: aerobic
Inoculum: domestic sewage, adapted
Concentration: 20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation: 82 % after 28 day(s)
Result: other: "inherently biodegradable" (adapted inoculum)

Method: other: Sturm Test, 14 d preacclimation followed by 28 d incubation, parameter: CO2 evolution.
Year: 1979
GLP: no data
Remark: 69% DOC removal
(64)

Type: aerobic
Inoculum: Pseudomonas aeruginosa (Bacteria)
Concentration: 500 mg/l related to Test substance
Degradation: 100 % after .6 day(s)

Method: other: medium: mineral medium, 30 degr. C, shaking, parameter: %MBAS removal.
Year: 1979
GLP: no data
(144)

Type: aerobic
Inoculum: other bacteria: Achromobacter guttatus
Concentration: 500 mg/l related to Test substance
Degradation: 100 % after 1.2 day(s)

Method: other: medium: mineral medium, 30 degr. C, shaking, parameter: %MBAS removal.
Year: 1979
GLP: no data
(144)

Type: aerobic
Inoculum: other bacteria: Flavobacterium devorans
Concentration: 500 mg/l related to Test substance

Degradation: 100 % after 1 day(s)

Method: other: medium: mineral medium, 30 degr. C, shaking, parameter: %MBAS removal.
Year: 1979
GLP: no data
(144)

Type: aerobic
Inoculum: other bacteria: Citrobacter freundii
Concentration: .5 g/l related to Test substance
Degradation: ca. 100 % after 1 day(s)

Method: other: medium: mineral medium, 32 degr. C, shaking, parameter: %MBAS removal.
Year: 1975
GLP: no data

Remark: At a concentration of 1.0 g/l degradation was 65% after 1 day. Data evaluated from graph.
(143)

Type: aerobic
Inoculum: other: river water
Concentration: 20 mg/l related to Test substance
Degradation: ca. 100 % after 3 day(s)

Method: other: medium: river water (Des Plaines river, USA), 25 degr. C, aerobic conditions, parameter: %MBAS removal.
Year: 1965
GLP: no data

Remark: Data evaluated from graph.
Degradation half-life: 0.5 - 1 day
(101)

Type: aerobic
Inoculum: other: seawater
Concentration: 20 mg/l related to Test substance
Degradation: 99 % after 3 day(s)

Method: other: medium: seawater from bay of Barcelona, Spain; 22 degr. C, shaking, parameter: %MBAS removal.
Year: 1987
GLP: no data
Test substance: other TS: SDS, purity 99.2%

Remark: Data evaluated from graph.
(162)

Type: aerobic
Inoculum: other: seawater
Concentration: 20 mg/l related to Test substance
Degradation: 92 - 95 % after 9 day(s)

Method: other: medium: seawater from bay of Cadiz, Spain; 22-28 degr. C, parameter: %MBAS removal.
Year: 1981
GLP: no data
Test substance: other TS: SDS, 30% active material
(135)

Type: aerobic
Inoculum: activated sludge
Concentration: 100 mg/l related to Test substance
Degradation: 100 % after 14 day(s)
Kinetic: 1 day(s) 8 %
2 day(s) 42 %
3 day(s) 59 %
5 day(s) 70 %
Method: other: test similar to the MITI-method in the OECD Guideline for Testing of Chemicals, Section 3; Degradation and Accumulation
Year: 1981
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Parameter: % BOD/TOD

(155)

Type: anaerobic
Inoculum: anaerobic sludge
Concentration: 10 mg/l related to Test substance
Degradation: 90.1 % after 28 day(s)

Method: other: anaerobic digester simulation test with uniformly 14C-labeled substance, 35 degr. C, parameter: 14C-gas evolution (CH4 & CO2).
Year: 1987
GLP: no data

(145)

3.6 BOD5, COD or BOD5/COD Ratio
-

3.7 Bioaccumulation

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 24 hour(s) at 18 degree C
Concentration: .25 mg/l
BCF: = 2.1
Elimination: yes

Method: other: flow-through test with radioactive test substance (35S-labeled sodium dodecyl sulfate).

Remark: Elimination: clearance time (ct 50) was ca. 100 h.
Maximum whole body accumulation was reached after 24 h. SDS was absorbed first mainly through the gills, and then distributed to internal organs by blood and finally concentrated in the gall bladder.
Test condition: 6 month old fish were used (average body weight of fish: 5.0 +- 0.87 g). No feeding for 2 to 3 days prior to and during test. Exposure to 35S-labeled sodium dodecyl sulfate in a continuous flow system for up to 72 h. Flow rate: 21.5 ml/min; water temperature: 20 - 23 degr.C
Elimination: fish were transferred in fresh water and kept for further 120 h (flow-through). Whole body radioactivity was counted with a liquid scintillation counter. Flow rate: 41 ml/min.

(165)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 24 hour(s) at 21 degree C
Concentration: .5 mg/l
BCF: ca. 5
Elimination: yes

Method: other: flow-through test with radioactive test substance (35S-labeled sodium dodecyl sulfate).

Remark: BCF evaluated from graph.
Clearance time (ct 50) was ca. 72 h. Elimination after 3 d in surfactant-free water was 50% for whole body, 60% for gall bladder and 80% for hepatopancreas.
Maximum whole body accumulation was reached after 24 h. SDS was finally concentrated in the gall bladder (BCF ca. 800 - 900).
Test condition: 7 - 10 month old fish were used (average body weight of fish: 4.2 +- 0.58 g). No feeding for 3 days prior to and during test. Exposure to 35S-labelled sodium dodecyl sulphate in a continuous flow system for up to 72 h. Water temperature: 19.5 - 23 degr. C; flow rate: 20.83 ml/min.
Elimination: fish were transferred in fresh water and kept for further 120 h (flow-through). Whole body radioactivity was counted with a liquid scintillation counter. Flow rate: 41.67 ml/min.

(164)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 120 hour(s) at 22 degree C
BCF: 3.9 - 5.3
Elimination: no data

Method: other: no further information retrievable
Year: 1981
GLP: no data
Test substance: other TS: SDS, 35S-labelled; no indication about purity
Remark: Concentrations of test substance were 2.7, 27, 400, 4000 and 40000 ug/l. The BCF was not affected by different concentrations.
Equilibrium was reached after 72 hr; the different exposure concentrations had no effect upon the BCF.

(166)

Species: other: Proterorhinus marmoratus (goby)
Exposure period: 240 day(s) at 15 degree C
Concentration: 4 mg/l
BCF: 7.15

Method: other: see Test Condition
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: 30 animals/experiment; water was changed once in every 2 days; salinity: 7.21 ppt; no feeding during test; 1 uCi/l 35S-

labelled SDS was added together with 4 mg/l unlabelled SDS. Fish were homogenized in 4 ml water after washing in water. (154)

3.8 Additional Remarks
-

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: flow through
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 7.97 -

Method: other: static test, 25 degr. C.
Year: 1977
GLP: no data
Test substance: other TS: SDS, laboratory grade, one year-old lot

Remark: LC50 [48h] = 8.81 mg/l
Nominal concentration.
(60)

Type: flow through
Species: Jordanella floridae (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 8.1 -

Method: other: static test, 25 degr. C.
Year: 1977
GLP: no data
Test substance: other TS: SDS, laboratory grade, one year-old lot

Remark: LC50 [48h] = 10.0 mg/l
Nominal concentration.
(60)

Type: flow through
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 5.3 -

Method: other: flow-through test, 13-17 degr. C, no aeration.
Year: 1975
GLP: no data
Test substance: other TS: SDS, laboratory grade

Remark: Mean result of several tests.
(125)

Type: flow through
Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 4.62 -

Method: other: static test, 15 degr. C.
Year: 1977
GLP: no data
Test substance: other TS: SDS, laboratory grade, one year-old lot

Remark: LC50 [48h] = 5.95 mg/l, LC50 [10d] = 2.85 mg/l.
Nominal concentration.
(60)

Type: other: no data
Species: Carassius auratus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 23.7 - 34.9

Method: other: No particulars on test method given.
GLP: no data
(41)

Type: semistatic
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 9.9 - 20.1

Method: other: see Test Condition
Year: 1982
GLP: no data
Test substance: other TS: SDS, purity 99.9%

Remark: toxicity range corresponds to stages of development:
adult (12.8 mg/l); juvenile (20.1 mg/l); fry (9.9 mg/l).
Test condition: 25 degr. C, renewal of test water twice daily.
(119)

Type: semistatic
Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 7 day(s)
Unit: mg/l Analytical monitoring: no
LC50: 1.8 -
Method: other: "Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms." EPA-600/4-87/028, U.S. EPA, Office Res. Devel. (May 1988).
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: Semistatic test (daily renewal), 7 day-old larvae, salinity: 32 ppt, daily feeding with newly hatched Artemia sp. nauplii.
(116)

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 46 -

Method: other: Japanese Industrial Standard (JIS) K 0102-1981; Testing Methods for Industrial Wastewater.
Year: 1981
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 after 6 h: 67 mg/l; LC50 after 24 h: 46 mg/l
Test condition: Water hardness: 25 mg/l CaCO3; 21 - 22 degr. C; pH 6.7 - 7.1; synthetic water; no feeding during test; no aeration; renewal of testing solution every 12 hours.
(96)

Type: semistatic
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 8 day(s)
Unit: mg/l Analytical monitoring: no
NOEC: 2.2 - 4.6
LC50: 4.8 - 5.9
LC10 : 4 - 4.5

Method: other: embryo-larval-test according to EPA-600/4-85/014 (daily renewal), 25 degr. C, parameter: mortality & growth (weight).
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity
Remark: Several assays
(126)

Type: semistatic
Species: Pimephales promelas (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 10.2 - 22.5

Method: other: see Test Condition
Year: 1982
GLP: no data
Test substance: other TS: SDS, purity 99.9%

Remark: toxicity range corresponds to stages of development: adult (22.5 mg/l); juvenile (17 mg/l); fry (10.2 mg/l).
Test condition: 25 degr. C, renewal of test water twice daily.
(119)

Type: semistatic
Species: Poecilia reticulata (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 13.5 - 18.3

Method: other: see Test Condition
Year: 1982
GLP: no data
Test substance: other TS: SDS, purity 99.9%

Remark: toxicity range corresponds to stages of development: adult (13.5 mg/l); juvenile (16.2 mg/l); fry (18.3 mg/l).
Test condition: 25 degr. C, renewal of test water twice daily.
(119)

Type: semistatic
Species: other: Cichlasoma nigrofasciatum (Convict cichlid)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 16.1 - 30

Method: other: see Test Condition

Year: 1982
GLP: no data
Test substance: other TS: SDS, purity 99.9%

Remark: toxicity range corresponds to stages of development: adult (30 mg/l); juvenile (25.2 mg/l); fry (16.1 mg/l).
Test condition: 25 degr. C, renewal of test water twice daily.
(119)

Type: semistatic
Species: other: Saccobranchus fossilis (fresh water fish)
Exposure period: 60 day(s)
Unit: mg/l Analytical monitoring: no data
NOEC: >= 2.24 -

Method: other: semistatic test
Year: 1981
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: No visible symptoms up to highest concentration tested (2.24 mg/l).

Other tested sublethal endpoints:
blood coagulation time: LOEC 1.12 mg/l NOEC 0.75 mg/l
increase of haematocrit values: LOEC 2.24 mg/l NOEC 1.12 mg/l
Test condition: Renewal of test solution every 48 h;
pH: 7.2 - 7.3
temperature: 22.2 +- 2.4 degr. C DO: 5.6 +- 0.6 mg/l total hardness: 60 +- 3 mg/l
(50)

Type: static
Species: Carassius auratus (Fish, fresh water)
Exposure period: 6 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: = 60 -

Method: other: see Test Condition
Year: 1974
GLP: no data
Test substance: other TS: SDS, purity 99%

Test condition: 20 degr. C, no aeration.
(62)

Type: static
Species: Cyprinodon variegatus (Fish, estuary, marine)
Exposure period: 7 day(s)
Unit: mg/l Analytical monitoring: no
LC50: 2.9 -
Method: other: "Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms." EPA-600/4-87/028, U.S. EPA, Office Res. Devel.

(May 1988).
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range: 1.8 - 3.4 mg/l.
Test condition: semistatic test (daily renewal), 7 day-old larvae, salinity: 32 ppt.
(116)

Type: static
Species: Cyprinodon variegatus (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 9 -

Method: ther: static test, 20 degr. C, daily feeding, salinity: 15 ppt, continuous aeration.
Year: 1974
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 [24h] = 10 mg/l, LC50 [48h] = 9 mg/l.
(7)

Type: static
Species: Cyprinodon variegatus (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: 4.1 -

Method: other: static test, 22 degr. C, salinity: 10 ppt, aeration. Test according to ASTM Committee E-35: "Standard Practices for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians." ASTM Des. No. E-729 (1980).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 3.83 - 4.47 mg/l.
(134)

Type: static
Species: Fundulus heteroclitus (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 5.6 -

Method: other: APHA (1965), 20 degr. C, salinity: 20 ppt, adaptation to artificial seawater for 10-14 d prior to test.
Year: 1970
GLP: no data
Test substance: other TS: SDS, reagent grade

Remark: LC50 [24h] = 5.6 mg/l, LC50 [48h] = 5.6 mg/l.
In a second assay: LC50 [96h] = 4.5 mg/l.
(102)

Type: static
Species: Fundulus heteroclitus (Fish, estuary, marine)
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 4.5 - 80

Method: other: No particulars on test method given.
Year: 1984
GLP: no data
Test substance: other TS: SDS, analytical grade

Remark: Toxicities (mg/l) depend on salinity: 80 (0 ppt); 52 (5.9 ppt); 26 (33.2 ppt); 4.5 (63 ppt). Three weeks adaptation to different salinities prior to test.
Test condition: Three weeks adaptation to different salinities of test waters, pH 7.2 - 7.3.
(115)

Type: static
Species: Fundulus heteroclitus (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 1.25 -

Method: other: static test, 20 degr. C, salinity: 20 ppt.
Year: 1979
GLP: no data
Test substance: other TS: SDS, no indication about purity
(110)

Type: static
Species: Fundulus similis (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: .51 -

Method: other: see Test Condition
Year: 1975
GLP: no data

Test substance: other TS: SDS, no indication about purity

Remark: In a second assay: LC50 = 1.8 mg/l.
Test condition: 20 degr. C, salinity: 20 ppt.
(110)

Type: static
Species: Fundulus similis (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 4.5 -

Method: other: static test, 20 degr. C, daily feeding.
Year: 1974
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 [24h] = 4.7 mg/l, LC50 [48h] = 4.7 mg/l.
(7)

Type: static
Species: Gasterosteus aculeatus (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: .51 -

Method: other: static test, 20 degr. C, salinity: 20 ppt.
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: In a second assay: LC50 = 4.2 mg/l.
Test condition: No further information about test conditions.
(110)

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: 4.5 -
Method: other: "Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians". EPA 660/3-75/009 (1975).
Year: 1981
GLP: no data
Test substance: other TS: SDS, purity 93.4%

Remark: 95% confidence limit = 4.2 - 4.8 mg/l.
(14)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: = 10 -
LC50: = 22 -
LC100: = 30 -

Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15 (test corresp. to OECD Guideline 203)
Year: 1978
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: No further information about test conditions.
(92)

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
LC0: = 20 -
LC50: = 25 -
LC100: = 30 -

Method: other: Bestimmung der Wirkung von Wasserinhaltsstoffen auf Fische, DIN 38412 Teil 15 (test corresp. to OECD Guideline 203)
GLP: no
Test substance: other TS: SDS, purity 90 - 95%

Remark: Test method conforms with OECD Guideline 203.
(73)

Type: static
Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 96 hour(s)

Unit: mg/l Analytical monitoring: no
LC50: 1.48 -
Method: other: Am. Soc. for Testing & Materials. "Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians". E729-88, Philadelphia, PA.
Year: 1988
GLP: no data
Test substance: other TS: SDS, laboratory grade

Remark: 95% confidence limit: 1.35 - 1.63
Test condition: 25 +- 2 degr. C; salinity: 20 ppt; feeding twice daily during test. Larvae were tested.

(67)

Type: static
Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 2.8 -

Method: other: static test, 20 degr. C, daily feeding, salinity: 20 ppt, continuous aeration.
Year: 1974
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 [48h] = 2.8 mg/l

(7)

Type: static
Species: Menidia beryllina (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: = 1.5 -

Method: other: static test, 20 degr. C, salinity: 20 ppt.
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: No further information about test conditions.

(110)

Type: static
Species: Menidia menidia (Fish, estuary, marine)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50: 2.8 -
Method: other: static test, 22 degr. C, salinity: 10 ppt, aeration. Test according to ASTM Committee E-35: "Standard Practices for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians." ASTM Des. No. E-729 (1980).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 2.55 - 2.98 mg/l.

(134)

```
Type:             static
Species:          Phoxinus phoxinus  (Fish, fresh water)
Exposure period:  24 hour(s)
Unit:             mg/l                    Analytical monitoring: no
LC50:             = 30.5 -

Method:           other: static test, 13 degr. C.
  Year:           1977
   GLP:           no data
Test substance:   other TS: SDS, analytical grade
                                                                  (106)

Type:             static
Species:          Pimephales promelas  (Fish, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                    Analytical monitoring: no data
LC50:             6.6 -

Method:           other: "Methods for Acute Toxicity Tests with Fish,
                  Macroinvertebrates, and Amphibians". EPA 660/3-75/009
                  (1975).
  Year:           1983
   GLP:           no data
Test substance:   other TS: SDS, no indication about purity

Remark:           95% confidence limit = 5.8 - 7.5 mg/l.
                  In a second assay: LC50 [96h] = 6.9 mg/l (5.3 - 90).
                                                                   (45)

Type:             static
Species:          Pimephales promelas  (Fish, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                    Analytical monitoring:
TLm :             5.1 - 5.9

Method:           other: static test, 25 degr. C, no aeration.
  Year:           1959
Remark:           toxicity depends on water hardness.
                                                                   (69)

Type:             static
Species:          Salmo gairdneri  (Fish, estuary, fresh water)
Exposure period:  96 hour(s)
Unit:             mg/l                    Analytical monitoring: no
LC50:             = 6.2 -

Method:           other: static test with stirring, 13-17 degr. C, no aeration.
  Year:           1975
   GLP:           no data
Test substance:   other TS: SDS, laboratory grade

Remark:           Mean result of several tests.
                                                                  (125)

Type:             static
Species:          other: Atherinops affinis (marine fish)
Exposure period:  96 hour(s)
Unit:             mg/l                    Analytical monitoring: no
LC50:             1.88 -
```

Method: other: Am. Soc. for Testing & Materials. "Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates, and Amphibians". E729-88, Philadelphia, PA.
Year: 1988
GLP: no data
Test substance: other TS: SDS, laboratory grade

Remark: 95% confidence limit: 1.67 - 2.11
Test condition: 20 +- 2 degr. C; salinity: 20 ppt; feeding twice daily during test. Larvae were tested.
(67)

Species: Cyprinus carpio (Fish, fresh water)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50: 60 -

Method: other: see Test Condition
Year: 1981
GLP: no data
Test substance: other TS: SDS, no indication about purity
Test condition: Test at 23 degr. C; no further information extractable (article in japanese).
(167)

Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
LC50: = 4.83 -

Method: other: static test, 20 degr. C, not further specified.

Remark: 95% confidence limit = 4.06 - 5.75 mg/l.
(131)

Species: Oryzias latipes (Fish, fresh water)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
TLm : = 10 -

Method: other: no further information retrievable (article in japanese).
(152)

Species: Salmo gairdneri (Fish, estuary, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
LC50: 4.5 - 8.6

Method: other: No particulars on test method given.
(41)

Species: other: Floridicthyes carpio (killifish)
Exposure period: 5 hour(s)
Unit: mg/l Analytical monitoring:
LC50: = 3 -

Method: other: No particulars on test method given.
(173)

Species: other: Macrones vittatus
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50: 1.39 - 1.53

Method: other: static test, 24 +- 3 degr. C, dissolved oxygen: 6.1 - 6.2 mg/l.
Year: 1978
GLP: no data
Remark: LC50 [48h] = 1.53 - 1.64 mg/l
Test substance: Test substances: Swascol 3L & Swascol 4L (both sodium dodecyl sulfate). No information about purities.
(160)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Artemia salina (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 1.5 -

Method: other: "Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians". EPA 660/3-75/009 (1975).
Year: 1983
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: Static test.
(45)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 19.1 -

Method: other: not further specified.
(156)

Species: Artemia salina (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 1.48 -

Method: other: static test, 20 degr. C, salinity: 20 ppt.
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: In a second assay: LC50 = 5.6 mg/l.
(110)

Species: Artemia salina (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 3.15 - 3.8
Method: other: static test, 20 degr. C, salinity: 34.5 ppt, 24h-old larvae.
Year: 1973
GLP: no data

Test substance: other TS: SDS, no indication about purity

Remark: Range due to various mixing methods.
(172)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: = 6.92 -

Method: other: static test, 24 degr. C, salinity: 30 ppt, larvae.
Year: 1980
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: With 3 to 4 month-old organisms: LC50 [48h] = 7.3 mg/l.
(39)

Species: Artemia salina (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: = 3.72 -

Method: other: static test, 24 degr. C, salinity: 30 ppt, larvae.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity
(38)

Species: Artemia salina (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 2.2 - 3.2

Method: other: static test, 24-30 degr. C, pH 7.9, salinity: 34 ppt, larvae.
Year: 1986
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: different parameters (temperature, salinity, pH) were tested and shown to have an influence on toxicity. EC50 (6 h) = 11 - 14 mg/l
(63)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: = 3.6 -

Method: other: static test, 24.5 degr. C, artificial seawater, parameter: movement of phyllopodia.
Year: 1974
GLP: no data
Test substance: other TS: SDS, no indication about purity
(130)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data

EC50: 13.3 - 19.9

Method: other: static test, 25 degr. C, salinity: 35 ppt, instar II-III larvae.
Year: 1981
GLP: no data
Test substance: other TS: SDS, purity >= 98%

Test condition: No further information about test conditions.
(159)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 14.8 - 18.5

Method: other: static test, 25 degr. C, salinity: 35 ppt, instar II-III larvae.
Year: 1980
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Range due to different geographical strains.
(157)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 20 - 22.5

Method: other: static test, 25 degr. C, salinity: 35 ppt, parameter: motility, ARC-test (Artemia Reference Center-test, Lab. Of Biol. Res. in Aquatic Poll., State University Ghent, Belgium).
Year: 1984
GLP: no data
Test substance: other TS: SDS, purity >= 98%

Remark: data from two international round robin exercises in Europe (59 laboratories, 143 measurements, mean LC50: 22.97 mg/l) and North America (7 laboratories, 21 measurements, mean LC50: 20.07 mg/l).
(158)

Species: Artemia salina (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 21.5 -

Method: other: static test, 25 degr. C, salinity: 35 ppt, parameter: motility, ARC-test (Artemia Reference Center-test, Lab. Of Biol. Res. in Aquatic Poll., State University Ghent, Belgium).
Year: 1989
GLP: no data
Test substance: other TS: SDS, purity >= 98%

Remark: 20 combinations of temperature and salinity were assayed. Both parameters had a highly significant influence on toxicity. Given EC50 is for standard ARC conditions. 95% confidence limit = 18.8 - 24.8 mg/l.

Test condition: No further information about test conditions.
(124)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 4.6 -

Method: other: "Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians". EPA 660/3-75/009 (1975).
Year: 1983
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit: 2.8 - 6.4 mg/l
In a second and third assay: LC50 [48h] = 4.8 mg/l (3.1 - 6.5) and 5.6 mg/l (3.3 - 8.2), respectively.
Test condition: Static test.
(45)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mmol/l Analytical monitoring: no
EC50: = .034 -

Method: other: AFNOR T.90301 (1974). Determination de l'inhibition de la mobilite de Daphnia magna Straus.
Year: 1986
GLP: no data
Test substance: other TS: SDS, analytical grade

Remark: 0.034 mmol/l = 9.8 mg/l.
(13)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 80 -

Method: other: AFNOR T.90301 (1974). Determination de l'inhibition de la mobilite de Daphnia magna Straus.
Year: 1974
GLP: no data
Test substance: other TS: SDS, reagent grade
(106)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 25 -

Method: other: According to Norme Francaise Homologue, NF T90-31 (1983)
(136)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: = 27.5 -

Method: other: Acute toxicity for Daphnia, EEC Directive 84/449, April 1984, 155-159.
Year: 1989
GLP: no data
Test substance: other TS: SDS, purity >= 98%

Remark: 16 combinations of temperature and water hardness were assayed. Both parameters had a highly significant influence on toxicity.
Given EC50 is for standard EEC conditions.
(124)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: 7 -
EC50: 28.6 -
EC100: 50 -

Method: other: DIN 38412, Teil 11 (Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse, Daphnia Kurzzeittest)
Year: 1974
GLP: no data
Test substance: other TS: SDS, purity 90 - 95%

Remark: Test method conforms with OECD Guideline 202 A.
(73)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 13.5 -

Method: other: Peltier, W., "Methods for Measuring the Acute Toxicity of Effluents to Aquatic Organisms". EPA 600/4-78-012; U.S. Environ. Prot. Agency, Environm. Monitor. and Support Lab., Cincinnati, OH.
Year: 1978
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Concentration of SDS checked after 24 h and 48 h by "chemical analysis" (no further information).
SDS was significantly biodegraded after 48 h.
LC50 (mg/l) was dependent on test temperature:

	24 h	48 h
20 degr. C	20.9	13.5
26 degr. C	12.9	10.8

Test condition: Static test at 20 and 26 degr. C; pH 8 - 8.5; no aeration.
(104)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 1.8 -

Method: other: according to "Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians". EPA 660/3-75-009 (1975). Flow-through test
Year: 1981
GLP: no data
Test substance: other TS: SDS, purity 93.4%

Remark: 95% confidence limit = 0.5 - 2.6 mg/l.
(14)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 6.2 - 9

Method: other: not further specified.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Three assays.
(103)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 7.8 -

Method: other: static test
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: Water hardness: 175 + 15 mg/l CaCO3, pH 8.1 +- 0.2
(103)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: = 23 -
EC50: 41 -
EC100: = 58 -
Method: other: static test, 20 degr. C, DIN 38412 part 11 (draft).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 38 - 44 mg/l.
(26)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 10.3 - 33

Method: other: static test, 20 degr. C, EPA-600/4-78/012
Year: 1985
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range of 8 replicate experiments (mean EC50 = 17.4 mg/l). EC50 [48h] = 5.4 - 15.0 (mean: 10.3 mg/l).
Food added at the beginning of test.
(105)

Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 6.3 -

Method: other: static test, 20 degr. C.
Year: 1973
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: EC50 (24 h) = 13.5 mg/l
(107)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: = 17 -
EC50: = 33 -
EC100: = 63 -

Method: other: static test, 20-22 degr. C.
Year: 1977
GLP: no
Test substance: other TS: SDS, no indication about purity
(22)

Species: Daphnia pulex (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 12.6 -

Method: other: Peltier, W., "Methods for Measuring the Acute Toxicity of Effluents to Aquatic Organisms". EPA 600/4-78-012; U.S. Environ. Prot. Agency, Environm. Monitor. and Support Lab., Cincinnati, OH.
Year: 1978
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Concentration of SDS checked after 24 h and 48 h by "chemical analysis" (no further information).
SDS was significantly biodegraded after 48 h.
LC50 (mg/l) was dependent on test temperature:

	24 h	48 h
20 degr. C	18.4	12.6
26 degr. C	13.9	10.2

Test condition: Static test at 20 and 26 degr. C; pH 8 - 8.5; no aeration.
(104)

Species: Daphnia pulex (Crustacea)
Exposure period: 48 hour(s)

Unit: mg/l Analytical monitoring: no data
EC50: 7.07 - 49.38

Method: other: Peltier, W.H. & Weber, C.W., EPA/600/4-85/013, Environmental Monitoring Support Laboratory, Cincinnati, Ohio (1985), p216. static test, 20-21 degr. C.
Year: 1987
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Three assays.
(114)

Species: Daphnia pulex (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 5 - 20.2
Method: other: static test, 20 degr. C [according to Peltier, W. "Methods for measuring the acute toxicity of effluents to aquatic organisms", EPA-600/4-78-012, Environm. Monitoring & Support Lab.; US Environmental Protection Agency (1978), 1 - 52]
Year: 1985
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range of 8 replicate experiments (mean EC50 = 15 mg/l). Values for 48 h: EC50 = 1.4 - 15.2 mg/l (mean EC50 = 8.9 mg/l; 10 replicate experiments).
(105)

Species: Gammarus pulex (Crustacea)
Exposure period: 4 day(s)
Unit: mol/l Analytical monitoring: no
EC50: .00001 - .00002

Method: other: static test, 20 degr. C.
Year: 1976
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 in mg/l: 3.6 - 4.6
Test condition: No further information about test conditions.
(17)

Species: Gammarus pulex (Crustacea)
Exposure period: 4 day(s)
Unit: mol/l Analytical monitoring: no
EC50: .00003 - .00005

Method: other: static test, 20 degr. C.
Year: 1978
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 in mg/l: 9.4 - 13.0
Test condition: No further information about test conditions.
(16)

Species: Mysidopsis bahia (Crustacea)
Exposure period: 7 day(s)
Unit: mg/l Analytical monitoring: no
EC50: 9.3 -
Method: other: "Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms." U.S. EPA-600/4-87/028 (1988)
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range: 5.3 - 14.5 mg/l.
Test condition: Semistatic test (daily renewal), salinity: 32 ppt, endpoint: survival.
(116)

Species: Mysidopsis bahia (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 6.1 -

Method: other: ASTM Des. No. E-729 (1980), static test, 22 degr. C, salinity: 20 ppt.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 5.02 - 7.48 mg/l.
In a second assay: EC50 = 7.1 mg/l.
(134)

Species: Mysidopsis bahia (Crustacea)
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 4.5 - 3.8

Method: other: according to APHA (1980) and ASTM (1980)
Year: 1986
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: semistatic test (renewal after 24 h), 25 degr. C, daily feeding, salinity: 30 ppt.
(150)

Species: Nitocra spinipes (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 12.2 - 17

Method: other: Static test; salinity: 7 ppt; 20-22 degr. C; no aeration.
Year: 1986
GLP: no data
Test substance: other TS: SDS, purity >= 99%
(149)

Species: Palaemonetes pugio (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no

EC50: = 108 -

Method: other: static test, 20 degr. C, daily feeding, salinity: 15 ppt.
Year: 1974
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LC50 [24h] = 135 mg/l, LC50 [48h] = 108 mg/l.
(7)

Species: Palaemonetes pugio (Crustacea)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 13.8 -

Method: other: static test, 20 degr. C, salinity: 20 ppt.
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: No further information about test conditions.
(110)

Species: other aquatic arthropod: Acanthomysis sculpta (mysid)
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: .94 - .96

Method: other: according to APHA (1980) and ASTM (1980)
Year: 1986
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: semistatic test (renewal after 24 h), 15 degr. C, daily feeding, salinity: 30 ppt.
(150)

Species: other aquatic arthropod: Acartia tonsa (Copepod)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: = .55 -

Method: other: ASTM Des. No. E-729 (1980).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 21 - 24% mortality in controls!
Test condition: static test, 22 degr. C, salinity: 10 ppt, no aeration.
(134)

Species: other aquatic arthropod: Chaoborus sp. (insecta diptera)
Exposure period: 4 day(s)
Unit: mol/l Analytical monitoring: no
LC50 : .00004 - .00006

Method: other: static test at 20 degr. C with larvae.
Year: 1976
GLP: no data

Test substance: other TS: SDS, no indication about purity

Remark: 0.0000417 - 0.0000603 mol/l = 12 - 17.3 mg/l
No further description of test method.
(17)

Species: other aquatic arthropod: Culex pipiens quinquefasciatus (mosquito)
Unit: mg/l Analytical monitoring:
LC50 : = 78 -

Method: other: test with pupae, method not further specified
Year: 1971

Remark: No data on exposure period.
Pupae drown due to reduction of surface tension.
(127)

Species: other aquatic arthropod: Eurytemora affinis (Copepod)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 2.6 -

Method: other: ASTM Des. No. E-729 (1980).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 8 - 20% mortality in controls!
95% confidence limit = 2.03 - 3.15 mg/l.
Test condition: static test, 22 degr. C, salinity: 10 ppt, no aeration.
(134)

Species: other aquatic arthropod: Homarus americanus (american lobster)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50 : .72 -

Method: other: static test in sea water at 20 degr. C; parameter: mortality (lack of heart beat)
Year: 1976
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 0.44 - 1.2 mg/l.
LC50 [48h] = 1.8 - 6.7 mg/l
Test condition: First stage larvae were tested. Feeding with brine shrimp nauplii every day (no removal of dead nauplii). Correction for mortality in controls.
(169)

Species: other aquatic arthropod: Mysidopsis almyra (mysid)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 2 -

Method: other: static test, 20 degr. C, daily feeding, salinity: 20 ppt.
Year: 1974
GLP: no data

Test substance: other TS: SDS, no indication about purity
(7)

Species: other aquatic arthropod: Neomysis americana (mysid)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
EC50: 5.7 -

Method: other: ASTM Des. No. E-729 (1980).
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 4.57 - 7.14 mg/l.
In a second assay: EC50 = 8.8 mg/l.
Test condition: static test, 22 degr. C, salinity: 20 ppt.
(134)

Species: other aquatic mollusc: Arbacia punctulata (sea urchin)
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 3.2 -

Method: other: "Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms." U.S. EPA-600/4-87/028 (1988)
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range: 2.6 - 5.1 mg/l.
Test condition: 1 h exposition of sperm cells, then addition of eggs; fertilization was stopped after 20 min. by addition of 10% buffered formaldehyde solution. Parameter: reduction in number of eggs fertilized.
(116)

Species: other aquatic mollusc: Corbicula fluminea (freshwater clam)
Exposure period: 5 day(s)
Unit: mg/l Analytical monitoring: yes
LC50 : 16.7 -

Method: other: flow-through test at 20 degr. C
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity
(65)

Species: other aquatic mollusc: Corbicula fluminea (freshwater clam)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
LC50 : 31.4 -

Method: other: static test at 18 - 20 degr. C
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 27.2 - 36.2 mg/l.
(65)

```
Species:        other aquatic mollusc: Crassostrea gigas (pacific oyster)
Exposure period:  48 hour(s)
Unit:             mg/l                  Analytical monitoring:
LC50 :            = 1 -

Method:           other: static test according to American Public Health
                   Association: Standard methods for the examination of water
                   and waste water; 14th Edition
  Year:           1976
Test substance:   other TS: SDS, no indication about purity

Remark:           Larvae were tested.
                                                                        (34)

Species:          other aquatic mollusc: Crassostrea gigas (pacific oyster)
Exposure period:  48 hour(s)
Unit:             mg/l                  Analytical monitoring: no
EC50:             = .84 -
LC50 :            = .91 -

Method:     other: static test at 20 degr. C; salinity: 29 ppt; parameter
                  for EC50: abnormal shell development
  Year:           1976
   GLP:           no data
Test substance:   other TS: SDS, 85% active ingredient

Remark:           Larvae were tested.
                  Mean values of several assays.
                                                                        (33)

Species:          other aquatic mollusc: Limnaea peregra (snail)
Exposure period:  6 day(s)
Unit:             mg/l                  Analytical monitoring: yes
LOEC :            .606 -

Method:           other: semi-static test (renewal every 24 h)
  Year:           1987
   GLP:           no data
Test substance:   other TS: SDS, 99% purity

Remark:           Endpoints were dry weight, organic matter and inorganic
                  matter of shells.
Test condition:   pH 7.1 +- 0.05, temperature: 22 +- 1 degr. C
                  Test organisms (3 month old) were kept for 18 days in
                  dechlorinated water after exposure.
                                                                       (148)
Species:          other aquatic mollusc: Lymnea palustris (snail)
Exposure period:  4 day(s)
Unit:             mol/l                 Analytical monitoring: no
LC50 :            .00002 - .00003

Method:           other: static test at 20 degr. C
  Year:           1976
   GLP:           no data
Test substance:   other TS: SDS, no indication about purity

Remark:           0.0000231 - 0.0000258 mol/l = 6.6 - 7.4 mg/l
                  No further description of test method.
                                                                        (17)
```

Species: other aquatic mollusc: Lymnea palustris (snail)
Exposure period: 4 day(s)
Unit: mol/l Analytical monitoring: no
LC50 : .00002 - .00003

Method: other: static test at 20 degr. C
Year: 1978
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 0.0000229 - 0.0000259 mol/l = 6.5 - 7.4 mg/l
No further description of test method.
(16)

Species: other aquatic mollusc: Protothaca staminea
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
EC50: .58 - .89

Method: other: no information about test method given
(40)

Species: other aquatic mollusc: Tresus capax (horse or gaper clam)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
LC50 : = .35 -

Method: other: static test according to American Public Health Association: Standard methods for the examination of water and waste water; 14th Edition
Year: 1976
Test substance: other TS: SDS, no indication about purity

Remark: High ratios of mortality (33 - 47%) in the controls!
Larvae were tested.
(34)

Species: other aquatic mollusc: Tresus sp.
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
EC50: .58 - .89

Method: other: no information about test method given

Remark: Tested species: Tresus capax and Tresus nuttalli.
(40)

Species: other aquatic worm: Arenicola marina (lugworm)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
LC50 : 15.2 -

Method: other: semistatic test (renewal after 24 h) at 15 degr. C; aeration
Year: 1987
Test substance: other TS: SDS, purity 99%

Remark: 95% confidence limit = 13.2 - 17.6 mg/l.
(44)

Species: other aquatic worm: Neanthes arenaceodentata (polychaet)
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no
LC50 : = 8 -

Method: other: according to APHA (1980) and ASTM (1980)
Year: 1986
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: static test at 21 - 23 degr. C; salinity: 35 ppt.
(150)

Species: other aquatic worm: Nereis virens (sandworm)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no
LC50 : = 13.5 -

Method: other: static test according to APHA (1965); 20 degr. C; salinity: 20 ppt; parameter: lethality.
Year: 1970
GLP: no data
Test substance: other TS: SDS, reagent grade
(102)

Species: other aquatic crustacea: "Dungeness crab"
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 8 -

Method: other: no information about test method given
(35)

Species: other aquatic crustacea: "spot shrimp"
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 5.8 -

Method: other: no information about test method given
(35)

Species: other: Brachionus calyciflorus (rotifer)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: 1.4 -

Method: other: according to US EPA-600/4-85-013
Year: 1991
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 1.1 - 1.6 mg/l.
(141)

Species: other: Brachionus plicatilis (rotifer)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = 4.47 -
LC50 : 5.42 -

Method: other: according to APHA (1985) and U.S. EPA-600/4-85/013, static test at 25 degr. C; salinity: 15 ppt.
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 5 - 5.8 mg/l.
(140)

Species: other: Brachionus plicatilis (rotifer)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = 2.58 -
LC50 : 4.42 -

Method: other: according to APHA (1985) and U.S. EPA-600/4-85/013, static test at 25 degr. C; salinity: 30 ppt
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 3.8 - 5.1 mg/l.
(139)

Species: other: Brachionus plicatilis (rotifer)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
LC50 : = 15.4 -

Method: other: static test at 25 degr. C; salinity: 35 ppt
Year: 1988
GLP: no data
Test substance: other TS: SDS, purity >= 98%

Remark: 16 combinations of temperature and salinity were assayed. Both parameters had a highly significant influence on toxicity. Given LC50 is for standard conditions.
(124)

Species: other: Brachionus rubens (rotifer)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no
NOEC: = .62 -
LC50 : 1.35 -

Method: other: according to APHA (1985) and U.S. EPA-600/4-85/013, static test at 25 degr. C; salinity: 30 ppt
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 1.12 - 1.58 mg/l.
(140)

Species: other: Chilomonas paramecium (saprozoic flagellate)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no
LOEC : = 26 -

Method: other: static test at 20 degr. C; parameter: growth measured with Couter counter
Year: 1980
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LOEC is effect concentration at which growth is reduced by 5% compared to untreated control (=TGK 5%).
(28)

Species: other: Entosiphon sulcatum (bacteriovorous flagellate)
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no
LOEC : = 40 -

Method: other: static test at 25 degr. C; parameter: growth measured with Coulter counter
Year: 1980
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LOEC is effect concentration at which growth is reduced by 5% compared to untreated control (=TGK 5%).
(27)

Species: other: Uronema parduczi (bacteriovorous flagellate)
Exposure period: 20 hour(s)
Unit: mg/l Analytical monitoring: no
LOEC : = .75 -

Method: other: static test at 25 degr. C; parameter: growth measured with Coulter counter
Year: 1980
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: LOEC is effect concentration at which growth is reduced by 5% compared to untreated control (=TGK 5%).
(24)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Microcystis aeruginosa (Algae, blue, cyanobacteria)
Endpoint: growth rate
Exposure period: 8 day(s)
Unit: mg/l Analytical monitoring: no
TGK 3% : = 7 -

Method: other: Static test; 27 degr. C; cell growth determined photometrically (OD 578nm). German norm DEV L 3 (1960)
Year: 1975
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: TGK = toxische Grenzkonzentration (toxic threshold concentration); concentration at which optical density of culture is >3% below control value.
(19) (20) (21)

Species: Scenedesmus quadricauda (Algae)
Endpoint: growth rate

Exposure period: 8 day(s)
Unit: mg/l Analytical monitoring: no
TGK 3% : .02 -

Method: other: static test, 25 degr. C, parameter: Growth (optical density at 436 nm)
Year: 1977
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: TGK = toxische Grenzkonzentration (toxic threshold concentration); concentration at which optical density of culture is >3% below control value.
The species was later identified as being Scenedesmus subspicatus (Dr. M. Pattard, WaBoLu-Institute, Berlin; personal communication). The toxicity threshold was fixed at 3% in this study; it is not clear, whether at the next higher concentrations statistically significant effects occured. Therefore, the test was repeated with the same species according to a standard guideline. The respective data are incorporated in this chapter.
(20) (21) (23)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring:
EC0: = 30 -
EC50: = 53 -
Method: other: DIN 38412, Teil 9: "Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen" (Algal growth inhibition test)
GLP: yes
Test substance: other TS: SDS, 96% purity
(75)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no
EC0: 30 -

Method: other: DIN 38412, Teil 9: "Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen" (Algal growth inhibition test)
Year: 1994
GLP: yes
Test substance: other TS: SDS, purity 96%

Remark: Test method conforms with OECD Guideline 201.
(76)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 80 -
EC20 : 15 -

Method: other: DIN/EN 28692

GLP: no
Test substance: other TS: SDS, purity 99% (Sigma)

Remark: Concentration of test substance was monitored via DOC analysis of the control without algae. No significant decrease of DOC was observed during the 96 h test.
(93)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 4 day(s)
Unit: mg/l Analytical monitoring: no data
EC10: 12 -
EC50: 117 -
EC90 : 200 -
Method: other: growth inhibition test
Year: 1990
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: reconstituted water; pH 7 - 7.5; 20 degr. C; inoculated to density of 10exp4 cells/ml; light intensity: 15 kLux; continuous aeration. Parameter: growth rate measured as OD at 600 nm.
(121)

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 8 day(s)
Unit: mmol/l Analytical monitoring: no
EC50: = .013 -

Method: other: static test, 24 degr. C, parameter: growth (measured by coulter counter).
Year: 1986
GLP: no data
Test substance: other TS: SDS, analytical grade

Remark: 0.013 mmol/l = 3.75 mg/l.
(13)

Species: Selenastrum capricornutum (Algae)
Endpoint: other: photosynthesis
Exposure period: 6 hour(s)
Unit: mg/l Analytical monitoring: no data
EC10: 140 -
EC50: 1550 -
EC90 : > 20000 -

Method: other: photosynthesis inhibition test
Year: 1990
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: reconstituted water; pH 7 - 7.5; 20 degr. C; light intensity: 21 kLux. After 4 h incubation with SDS NaHC14O3 was added and further incubated for 2 h. Parameter: measurement of incorporated radioactivity.
(121)

Species: Skeletonema costatum (Algae)
Endpoint: other: incorporation of radioactivity (source: NaH14CO3) and chlorophyll a content.
Exposure period: 2 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 2.33 -

Method: other: AAP (US/EPA): Algal Assay Procedure bottle test. National Eutrophication Research Programme, EPA, August 1971.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 1.57 - 3.54 mg/l.
Test condition: Static test, 22 degr. C, salinity: 20 ppt.
(134)

Species: other algae: Prorocentrum minimum
Endpoint: other: incorporation of radioactivity (source: NaH14CO3) and chlorophyll a content.
Exposure period: 2 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 1.32 -

Method: other: AAP (US/EPA): Algal Assay Procedure bottle test. National Eutrophication Research Programme, EPA, August 1971.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 0.22 - 3.42 mg/l.
Test condition: Static test, 22 degr. C, salinity: 20 ppt.
(134)

Species: other algae: Pseudoisochrysis paradoxa
Endpoint: other: incorporation of radioactivity (source: NaH14CO3) and chlorophyll a content.
Exposure period: 2 hour(s)
Unit: mg/l Analytical monitoring: no
EC50: = 1.27 -

Method: other: AAP (US/EPA): Algal Assay Procedure bottle test. National Eutrophication Research Programme, EPA, August 1971.
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: 95% confidence limit = 0.09 - 13.4 mg/l.

Test condition: Static test, 22 degr. C, salinity: 20 ppt.
(134)

Species: other aquatic plant: Champia parvula (red macroalga, marine species)
Endpoint: other: fertilization (development of cystocarps)
Exposure period: 2 day(s)
Unit: mg/l Analytical monitoring: no
EC50: .3 -

Method: other: "Short-term Methods for Estimating the Chronic Toxicity of Effluents and Receiving Waters to Marine and Estuarine Organisms." EPA-600/4-87/028
Year: 1989
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Toxicity range: 0.2 - 0.4 mg/l.
Test condition: static test; 2 d exposition followed by 5-7 d incubation without toxicant.
(116)

Species: other aquatic plant: Lemna minor (duckweed)
Endpoint: other: root length and dry weight
Exposure period: 7 day(s)
Unit: mg/l Analytical monitoring: yes
EC50: 18 -

Method: other: flow-through test at 21-23 degr. C
Year: 1981
GLP: no data
Test substance: other TS: SDS, purity 93.4%
(14)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: activated sludge
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: > 500 -

Method: ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year: 1981
GLP: no data
Test substance: other TS: SDS, 99% pure
Remark: The concentration of suspended solids in the sludge was 1500 mg/l.
Test condition: Parameter: respiration rate determined with oxygen electrode after 3 h incubation under aeration.
(98)

Type: aquatic
Species: activated sludge
Exposure period: 4 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 24 -

Method: other: inhibition of nitrification of activated sludge
Year: 1984
GLP: no data
Test substance: other TS: SDS, 99% pure

Remark: The concentration of suspended solids in the sludge was 1500 mg/l.
Test condition: Parameter: inhibition of production of oxidized nitrogen (nitrite plus nitrate), 4 h incubation.
(98)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 106 -

Method: other: 22 degr. C, parameter: reduction of INT (2-iodophenol, 3-nitro- phenol, 5-phenyl tetrazoliumchloride) by dehydrogenase activity of sludge (spectrophotometric measurement at 460 nm).
(54)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 130 -

Method: other: Activated Sludge, Respiration Inhibition Test, OECD Guideline 209, 4.04.1984

Remark: 95% confidence limit = 110 - 150 mg/l.
EC50 (30 min) = 170 mg/l (95% confidence limits: 150 – 190 mg/l). Test description incomplete.
(56)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 349 - 635

Method: other: OECD activated sludge respiration inhibition test, OECD Chemicals Programme, Ecotoxicological Testing, 1981.
(99)

Type: aquatic
Species: activated sludge, domestic
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 48 -

Method: other: TTC-test, 37 degr. C, parameter: reduction of TTC (triphenyl- tetrazoliumchloride) by dehydrogenase activity of sludge (spectro photometric measurement).

Remark: pH = 7.5 +- 0.5
(53)

Type: aquatic
Species: Aeromonas hydrophila (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 3700 -

Method: other: static test, 37 degr. C, parameter: growth (OD 650 nm).
(51)

Type: aquatic
Species: Escherichia coli (Bacteria)
Exposure period: 1 hour(s)
Unit: mg/l Analytical monitoring:
EC50: 273 - 427

Method: other: beta-galactosidase biosynthesis assay at 35 degr. C: incubate with toxicant for 30 min, then add enzyme inducer (IPTG), incubate further 30 min, measure enzyme activity by photometric test (420 nm).

Remark: Parameter: inhibition of enzyme biosynthesis.
(55)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring: no
EC50: .72 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt, pH 7.0 +- 0.5
Year: 1986
GLP: no data
Test substance: other TS: SDS, purity >= 99%
(149)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.8 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt, pH = 6.5-6.7
(51) (52) (53)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mmol/l Analytical monitoring: no
EC50: .007 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt.
Year: 1986
GLP: no data
Test substance: other TS: SDS, analytical grade

Remark: 0.007 mmol/l = 2 mg/l.
(13)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.19 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt.

Remark: Coefficient of variation: 0.33
(111)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.6 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt.

Remark: 95% confidence limit = 1.5 - 1.7 mg/l.
(56)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.8 -

Method: other: Bacterial luminescence test (Microtox test according to Beckman Manual); 15 degr. C; salinity: 20 ppt.
(10)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.6 -

Method: other: Bacterial luminescence test (Microtox test according to Microbics Corp.); 15 degr. C; salinity: 20 ppt.
(29) (30) (31)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.5 -

Method: other: Bacterial luminescence test (Microtox test according to Microbics Corp.); 15 degr. C; salinity: 20 ppt.
(32)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring: no data
EC50: 1.5 -

Method: other: Bacterial luminescence test (Microtox test); 15 degr. C
Year: 1982
GLP: no data
Test substance: other TS: SDS, 99% pure
(98)

Type: aquatic

Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 15 minute(s)
Unit: mg/l Analytical monitoring:
EC20 : .38 - .53

Method: other: Bacterial luminescence test (Microtox test); 15 degr. C; salinity: 20 ppt.

Remark: EC20 in water from Gulf of Mexico (salinity: 35 ppt): 0.81 - 0.97 mg/l.
(8)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 39 -

Method: other: Bacterial luminescence test (Microtox test); 15 degr. C; salinity: 20 ppt; exponentially growing cells used instead of freeze-dried powder.
(163)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring:
EC50: .8 -

Method: other: Bacterial luminescence test (Microtox test); no further particulars mentioned.
(136)

Type: aquatic
Species: Photobacterium phosphoreum (Bacteria)
Exposure period: 5 minute(s)
Unit: mg/l Analytical monitoring:
EC50: 1.2 -

Method: other: Bacterial luminescence test (Microtox test); room temperature; salinity: 20 ppt.
(146)

Type: aquatic
Species: Pseudomonas fluorescens (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 1650 -

Method: other: static test, 37 degr. C, parameter: growth (OD 650 nm).
(52)

Type: aquatic
Species: Pseudomonas fluorescens (Bacteria)
Exposure period: 18 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 1700 -

Method: other: static test, 37 degr. C, parameter: growth (OD 650 nm).
(51)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l Analytical monitoring:
EC10: = 905 -
EC<10 : = 271.5 -

Method: other: DIN 38412 Teil 8: "Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Bakterien." (cell multiplication inhibition test)
(74)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/l Analytical monitoring:
EC<10 : > 9050 -

Method: other: DIN 38412, Teil 27: "Bestimmung der Hemmwirkung von Abwasser auf die Sauerstoffzehrung von Pseudomonas putida." (respiration inhibition test)
(74)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l Analytical monitoring:
TGK 3% : = 290 -

Method: other: static test, 25 degr. C, parameter: growth (optical density).

Remark: Method by Bringmann & Kuehn.
TGK = toxische Grenzkonzentration (toxic threshold concentration); concentration at which optical density of culture is >1% below control value.
(25)

Type: aquatic
Species: other bacteria: Spirillum volutans
Exposure period: 2 hour(s)
Unit: mg/l Analytical monitoring:
EC90 : = 43 -

Method: other: parameter: reversal of flagellar rotation.

Remark: No description of method. Cited reference for method: Dutka, B.J. et al., Wat. Res. 17 (1983), 1363-1368.
(51)

Type: aquatic
Species: other bacteria: Spirillum volutans
Exposure period: 2 hour(s)
Unit: mg/l Analytical monitoring:
EC90 : = 4.15 -

Method: other: parameter: reversal of flagellar rotation.

Test condition: pH = 6.5 - 6.7
(53)

```
Type:             aquatic
Species:          other bacteria: heterogenous culture (multispecies)
Unit:             mmol/l                Analytical monitoring:
EC50:             = 3 -

Method:           other: 25 degr. C, parameter: heat flux determined with flow
                   micro- calorimeter.

Remark:           3 mmol/l = 865 mg/l.
                  No information about test duration.
                                                                        (13)


Type:             aquatic
Species:          other bacteria: mixed bacterial culture (Polytox, Polybac
                  Corp.)
Exposure period:  20 minute(s)
Unit:             mg/l                  Analytical monitoring:
EC50:             420 - 535

Method:           other: respiration inhibition test
                                                                        (56)

Type:             aquatic
Species:          other bacteria: river water & sediment (microcosm)
Exposure period:  1 hour(s)
Unit:             mg/l                  Analytical monitoring:
EC50:             > 1000 -

Method:         other: 24 degr. C, parameter: incorporation of 14C-acetate "into
                   microbial lipids" and glucosidase activity.
                                                                        (12)

Type:             aquatic
Species:          other bacteria: secondary sewage effluent
Exposure period:  5 day(s)
Unit:             mg/l                  Analytical monitoring: no data
EC50:             > 500 -

Method:           other: BOD5-method
  Year:           1984
   GLP:           no data
Test substance:   other TS: SDS, 99% pure

Test condition:    Standard amount of biodegradable substrate added (glucose &
                   glutamic acid at 3 mg/l each); dilution water inoculated with
                   sewage effluent at 2 ml/l; 5 d incubation in the dark at 20
                   degr. C; oxygen uptake measured titrimetrically.
                                                                        (98)

Type:             aquatic
Species:          other bacteria: secondary sewage effluent
Exposure period:  6 hour(s)
Unit:             mg/l                  Analytical monitoring: no data
EC50:             352 -

Method:           other: inhibition of growth of sewage microorganisms
  Year:           1984
   GLP:           no data
Test substance:   other TS: SDS, 99% pure
```

Test condition: 6 h incubation using 30% inoculum of settled sewage; 20 degr. C; parameter: absorbance at 620 nm.
(98)

Type: aquatic
Species: other bacteria: secondary sewage effluent
Exposure period: 16 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: 545 -

Method: other: inhibition of growth of sewage microorganisms
Year: 1984
GLP: no data
Test substance: other TS: SDS, 99% pure

Test condition: 16 h incubation using 10% inoculum of sewage effluent; 20 degr. C; parameter: absorbance at 620 nm.
(98)

Type: aquatic
Species: other fungi: Olpidium brassicae (fungus)
Unit: Analytical monitoring: no data

Method: other: see Test Condition
Year: 1979
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: All zoospores were dead after 270 min. exposition to a 1 mg/l solution of SDS. Parameter: motility of zoospores.
Test condition: Zoospores isolated from infected lettuce roots were incubated at 4 degr. C in mineral nutrient solution containing test substance and obserced microscopically.
(153)

Type: other: solid, Agar-based media
Species: other fungi: Podospora anserina
Exposure period: 5 day(s)
Unit: mg/l Analytical monitoring:
EC50: = 58 -

Method: other: static test at 26 degr. C; minimal medium; parameter: diameter of colonies
(108)

Species: activated sludge, domestic
Exposure period: 3 hour(s)
Unit: mg/l Analytical monitoring:
EC50: = 135 -

Method: other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192, Draft 1981

Remark: EC50 (30 min) = 188 mg/l, pH = 7.5 +- 0.2
(53)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish
-

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Endpoint: mortality
Exposure period: 40 day(s)
Unit: mg/l Analytical monitoring: no
NOEC: = 2 -

Method: other: according to EPA-600/3-75-009
Year: 1982
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Daphnids were <24 h old at the initiation of exposure and were exposed to the pollutant for 10 days. After 10 days, the next generations exposure was initiated with offspring produced at the respective exposure level. The test was conducted for 4 generations. Endpoint was survival of parental organisms.
No adverse effects on reproduction were observed at 2 mg/l.
Test condition: Semistatic test (renewal 3 times/week), water hardness: 175 + 15 mg/l CaCO3, pH 8.1 +- 0.2
(103)

Species: other: Hydra attenuata
Endpoint: other: budding rate
Exposure period: 21 day(s)
Unit: mg/l Analytical monitoring: no
NOEC: = 5.8 -

Method: other: semistatic test (renewal 3 times/week) at 20 degr. C
Year: 1975
GLP: no data
Test substance: other TS: SDS, purity 99.9%
(18)

Species: other aquatic arthropod: Ceriodaphnia dubia
Endpoint: other: mortality of parents and number of progeny/parent
Unit: Analytical monitoring: no data

Method: other: "Three Brood Ceriodaphnia Test", see Test Condition
Year: 1990
GLP: no data
Test substance: other TS: SDS, purity 99.9%

Remark: Results of three independent tests (values in brackets: 95% confidence intervals):

	LC50 [mg/l]	EC50 [mg/l]	NOEC [mg/l]
first test	38.7 (30-50) after 6 d	35.5 (10-61) after 6 d	6.48
second test	40.9 (30-50) after 5 d	36.3 (14-58) after 5 d	10.8

third test	42.2 (35-49) after 6 d	35.4 (16-55) after 6 d	10.8
Mean	40.6 (32-50)	35.7 (13-58)	9.4

Test condition: Reconstituted water; 26.2 +- 0.5 degr. C; pH 8.2 +- 0.1; hardness: 94.4 +- 0.1 mg/l CaCO3; endpoints: mortality of parent animals (LC50) and total number of progeny/parent (EC50). Length of test is governed by when the control animals have three broods.
Test was repeated 3 times at 3 week intervals.

(49)

Species: other aquatic arthropod: Ceriodaphnia dubia
Endpoint: other: mortality of parents and number of progeny/parent
Unit: Analytical monitoring: no data

Method: other: "Three Brood Ceriodaphnia Test", see Test Condition
Year: 1991
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: Data evaluated from graph:

LC0 [mg/l]	LC50 [mg/l]	EC50 [mg/l]	NOEC [mg/l]
ca. 30	ca. 40	ca. 36	ca. 9

Test condition: Reconstituted water; pH 8.4 - 9.0; hardness: 92 - 118 mg/l CaCO3; endpoints: mortality of parent animals (LC50) and total number of progeny/parent (EC50). Length of test is governed by when the control animals have three broods (7.6 d +- 1).

(48)

Species: other aquatic mollusc: Corbicula fluminea (freshwater clam)
Endpoint: other: respiration inhibition
Exposure period: 30 day(s)
Unit: mg/l Analytical monitoring: yes
NOEC: .65 -
LOEC: 3 -

Method: other: flow-through test, 20 degr. C
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: other endpoints tested:

total free amino acids and composition of specific free amino acids:
NOEC: 000.65 mg/l
LOEC: 0.65 mg/l

"condition index" (dry weight / shell length x 100):
NOEC: 0.65 mg/l
LOEC: 3 mg/l

Respiration inhibition was measured as reduction in the

oxygen consumption as compared to untreated controls. Exposure to 3 mg/l SDS for 5 and 30 days caused a significant reduction in wet-weight-normalized oxygen consumption rates; however, the reduction was not significant when normalized to dry weight. After 60 days of exposure to 0.65 and 3 mg/l SDS there were no significant differences in oxygen consumption rates.
(65)

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms
-

4.6.2 Toxicity to Terrestrial Plants

Species: other terrestrial plant: Zea mays (maize)
Endpoint: growth

Method: other: see Remark
Year: 1973
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: The influence of SDS on growth of maize in "brown forest soil" and "washed sand" was studied. Studied parameters were length and dry weight of seedlings. Effects ranged from 119% to 179% for seedlings watered at 1 g SDS/l as compared to untreated controls.
(118)

Species: other terrestrial plant: Secale cereale (rye)
Endpoint: growth

Method: other: see Remark
Year: 1972
GLP: no data
Test substance: other TS: SDS, no indication about purity

Remark: The influence of SDS (5 kg/ha) on growth of rye in "carbonate-rich brown forest soil" was studied. Parameter: harvest yield. Yield was 118% of untreated controls.
(118)

Species: other terrestrial plant: Lupinus albus
Endpoint: other: primary root length of seedlings
Expos. period: 2 day(s)
Unit: mg/l
EC50: = 384 -
LOEC : = 288 -

Method: other: static test at 20-25 degr. C
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity
Test condition: 70-90% relative humidity; 12 h day / 12 h night; seeds were allowed to germinate ca. 90 h prior to test.
(138)

Species: other terrestrial plant: Cicer arietinum
Endpoint: other: primary root length of seedlings
Expos. period: 2 day(s)
Unit: mg/l
EC50: = 361 -
LOEC : = 288 -

Method: other: static test at 20-25 degr. C
Year: 1988
GLP: no data
Test substance: other TS: SDS, no indication about purity

Test condition: 70-90% relative humidity; 12 h day / 12 h night; seeds were allowed to germinate ca. 90 h prior to test.
(138)

4.6.3 Toxicity to Soil Dwelling Organisms
-

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species
-

4.7 Biological Effects Monitoring
-

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

Remark: Geodia cydomium (sponge), 14 degr. C, static test, 17 h
At concentrations of 0.1 mg/l and above, the uptake of thymidine, uridine, and phenylalanine into the acid-soluble sponge fraction decreased.
(171)

Remark: Isolated gills of Anguilla anguilla L. (eel) were cannulated with polythene tubing and perfused with noradrenaline, sodium dodecyl sulfate (SDS) and combinations of both. SDS inhibited noradrenaline induced vasodilation: the maximum effect produced by noradrenaline was reduced by 40% in the presence of 0.000021 mmol/l SDS (= 0.006 mg/l) and by 60% in the presence of 0.00021 mmol/l SDS (= 0.06 mg/l). The inhibition appeared to be non-competitive and was reversible at very low (0.006 mg/l) detergent concentrations. In the absence of noradrenaline perfusate SDS concentrations of 0.3 mg/l and above produced vasoconstriction; lower concentrations had
(142)

Remark: Metabolism of sodium dodecyl sulfate by the detergent-degrading bacterium Pseudomonas C12B has been studied using a 14C radiotracer in combination with radio-respirometry, radio-TLC and GLC. Metabolism was extensive with 70% of the

radiolabel released as 14CO2 at completion. The remainder of the radiolabel was incorporated almost totally into cells. Ether extraction of cells indicated that 14C-labeled cellular material appearing early in the uptake process was predominantly ether-extractable (mainly 1-dodecanol) and was subsequently converted to more polar metabolites. Analysis of the extractable lipids established the sequential production from [1-14C] SDS of 1-dodecanol, dodecanal and dodecanoic acid. At this point the pathway diverged leading either to formation of 14CO2 via beta-oxidation or to elongation to C14, C16 and C18 fatty acyl residues with rapid incorporation into lipid fractions such as phospholipids. The pathway was correlated with known long-chain alkylsulfatases and alcohol dehydrogenases in this isolate and indicated that hydrophobic metabolites of the alkyl chain of surfactants can be incorporated into cellular components such as membrane lipids without prior degradation by beta-oxidation.

Test substance: [1-14C]-sodium dodecyl sulfate, radiochemical purity >99% by TLC.

(151)

Remark: Ilyanassa obsoleta (marine snail)
During embryogenesis polar lobes (anucleate vegetal poles) are formed, which serve as a mechanism for shunting morphogenetic determinants to one cell during the first two cleavages resulting in a very unequal four-cell stage.
Treatment of embryos with concentrations between 15 & 30 mg/l SDS inhibited polar lobe formation, but not cleavage, resulting in two equal cells. Concentrations <= 15 mg/l did not affect polar lobe formation.

Test substance: SDS, BioRad electrophoresis grade

(132)

5.0 Toxicokinetics, Metabolism and Distribution
-

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Value: = 1290 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: male/female
(168)

Type: LD50
Species: rat
Value: = 1400 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: male
(77)

Type: LD50
Species: rat
Value: = 977 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: female
(77)

Type: LD50
Species: rat
Value: = 200 - 2000 mg/kg bw

Method: Directive 84/449/EEC, B.1 "Acute toxicity (oral)"
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
(89)

5.1.2 Acute Inhalation Toxicity
-

5.1.3 Acute Dermal Toxicity

Type: LD50
Species: rabbit
Value: = 580 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
(36)

Type: LD50
Species: guinea pig
Value: > 1200 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
(36)

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Route of admin.: i.p.
Value: = 210 mg/kg bw

GLP: no data
Test substance: as prescribed by 1.1 - 1.4
(57)

Type: LD50
Species: rat
Route of admin.: i.v.
Value: = 118 mg/kg bw

GLP: no data
Test substance: as prescribed by 1.1 - 1.4
(37)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: rabbit
Result: irritating
EC classificat.: irritating

Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: 25 % concentration was tested
(78) (86)

Species: rabbit
Result: irritating

Method: Draize Test
Year: 1944
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Test concentrations of 2, 10 and 20 % were applied for 24 hours. The 2 % of the test substance gave score 5.2, the 10 % was scored 6.0, and the 20 % concentration also yielded the score 6.0 (max. score index = 8).
(42)

Species: rabbit
Result: irritating

Method: other: according OECD 404
GLP: no
Test substance: as prescribed by 1.1 - 1.4
(83)

Species: rabbit
Result: slightly irritating

Method: other: according OECD 404
GLP: no
Test substance: as prescribed by 1.1 - 1.4
(83)

Species: other: hairless mouse
Result: highly irritating
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: The substance was applied twice daily to the same area of skin and gently massaged into it.
(85)

5.2.2 Eye Irritation

Species: rabbit
Result: irritating

Method: Draize Test
Year: 1959
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: 10 % concentration was tested according to Draize criteria. One to 24 hours moderately irritating, at 7 days mildly irritating
(42)

Species: rabbit
Result: irritating

Method: Draize Test
Year: 1959
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: 20 % concentration was tested according to Draize criteria. At 24 hours severely irritating. At 7 days mildly irritating.
(42)

Species: rabbit

Result: irritating

Method: Draize Test
Year: 1959
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: 100 % compound was tested. Corneal opacity (present in one animal to day 35), vacuolization, iritis, red, swollen conjunctivae in all 3 animals.
(46)

Species: rabbit
Result: slightly irritating

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Sodiumlaurylsulfate in concentrations up to 2 % (0.5, 1.0, 2.0%) was tested and found to be not or only slightly irritating to the eye.
(95)

Species: rabbit
Result: highly irritating

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Sodiumlaurylsulfate in concentrations of 5% and higher (5, 10, 20%) was tested and found to be irritating or highly irritating to the eye.
(84) (95)

Species: rabbit
Result: highly irritating
EC classificat.: irritating

Method: Draize Test
Year: 1959
GLP: no
Test substance: other TS

Remark: Max. Draize score 42; Total score (M3 + 1 level): Severely irritating.
Source: Akzo Nobel Chemicals (NL)
Test substance: C12-alkyl sulphate, Na-salt (14.4 % in water)
(6)

Species: rabbit
Result: highly irritating
EC classificat.: irritating

Method: Draize Test
Year: 1959
GLP: no
Test substance: other TS

Remark: Max. Draize score 61 (was for one of six rabbits on day 7). Effects have not vanished in 5 rabbits at day 7.

Total score: Moderately irritating (M2 + 1 level)
Source: Akzo Nobel Chemicals (NL)
Test substance: C12-alkyl sulphate, Na-salt (14.3 % in water)
(6)

Species: rabbit
Result: highly irritating
EC classificat.: risk of serious damage to eyes

Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Dauerkontakt, not rinsed
(87)

Species: rabbit
Result: highly irritating

Method: Draize Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Dauerkontakt, not rinsed
(84)

Species: rabbit
Result: irritating

Method: Draize Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Dauerkontakt, not rinsed
(84)

Species: rabbit
Result: not irritating

Method: Draize Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4

(82)

Species: rabbit
Result: slightly irritating
Method: Draize Test
GLP: no
Test substance: as prescribed by 1.1 - 1.4
(82)

5.3 Sensitization

Type: Open epicutaneous test
Species: guinea pig
Result: ambiguous

Method: other: not specified
GLP: no data
Test substance: other TS

Remark: It was demonstrated that guinea pigs became sensitive to nickel and chromium when this agents were mixed with sodium lauryl sulfate. Paintings with sodium lauryl sulfate, potassium dichromate and nickel sulfate produced mild to no reactions. Animals painted with the mixtures, however, showed scaling, erythema, and infiltration (1). Alkyl- sulfates alone possess no worth mentioning sensitization potential (2).
Test substance: Sodium lauryl sulfate in conjunction with other substances, e. g. heavy metals.

(1)

5.4 Repeated Dose Toxicity

Species: rat Sex: no data
Strain: other: Albino
Route of administration: oral feed
Exposure period: 4 months
Frequency of treatment: continuous
Post exposure period: not specified
Doses: 2.0, 4.0, 8.0 %
Control Group: no data specified
NOAEL: = 2000 mg/kg bw
LOAEL: = 4000 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The NOAEL- and LOAEL-values given were calculated using the following parameters: NOAEL = 2% in diet, LOAEL = 4% in diet, 25 g diet/day, 250 g body weight.
Result: 2 %: slight but not significant growth retardation;
4 %: significant growth retardation;
8 %: lethal within two weeks, with severe diarrhea and bloating of the intestines.
Tissues were not examined microscopically.

(59) (80)

Species: rat Sex: male/female
Strain: other: Carworth Farm 'E' strain
Route of administration: oral feed
Exposure period: 13 weeks
Frequency of treatment: continuous
Post exposure period: not specified
Doses: 40, 200, 1000, 5000 ppm with respect to active substance
Control Group: yes
NOAEL: = 100 mg/kg bw
LOAEL: = 500 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The NOAEL- and LOAEL-values given were calculated using the following parameters: NOAEL = 1.000 ppm in diet, LOAEL = 5.000 ppm in diet, 25 g diet/day, 250 g body weight.
Result: 500 mg/kg/day: increased liver weights in females
Test substance: Sodium lauryl sulfate with 86% active material was tested.
(168)

Species: rat Sex: no data
Strain: Osborne-Mendel
Route of administration: oral feed
Exposure period: 2 years
Frequency of treatment: continuous (food ad libitum)
Post exposure period: not specified
Doses: 0.25, 0.5, 1,0 %
Control Group: no data specified
NOAEL: >= 1000 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: no data
Remark: The NOAEL-value given was calculated using the following parameters: NOAEL = 1% in diet, 25 g diet/day, 250 kg body weight. No LOAEL-value was determined. Due to the facts that the test substance was not identified, that the study was not conducted according to GLP, and that a LOAEL-value was not determined, the test is not considered relevant for a risk assessment.
Result: During the administration period weight gains were normal. Tissues taken at necropsy were free of gross and of microscopic abnormalities.
Test substance: Sodium dodecyl sulfate of unspecified quality was tested.
(59) (80)

Species: rat Sex: male
Strain: no data
Route of administration: drinking water
Exposure period: 5 months
Frequency of treatment: continuous
Post exposure period: not specified
Doses: 0.0, 0.05, 0.25 %
Control Group: yes
NOAEL: = .05 %
LOAEL: = .25 %

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: It was not possible to calculate a NOEAL-value in mg/kg/day from this study, because no data for the amount of water drunk per day was given. This study is not considered relevant for risk assessment.
Result: At 0.25 % the weights of the lung and kidney were increased. The hepatic triglyceride concentration was increased but the serum triglyceride concentration decreased.
(61)

Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: gavage

Exposure period: 28 days
Frequency of treatment: daily, 5 days/week
Post exposure period: 29 days (control and highest dose only)
Doses: 0, 30, 100, 300, 600 mg/kg
Control Group: yes
NOAEL: = 100 mg/kg bw
LOAEL: = 300 - 600 mg/kg bw
Method: other: Directive 79/831/EEC
Year: 1979
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Test substance: The sodium dodecyl sulfate tested consisted of 90 % active material, Texapon K 12

(100) (123) (129)

Species: dog Sex: male/female
Strain: Beagle
Route of administration: oral feed
Exposure period: 1 year
Frequency of treatment: access to food ad libitum
Post exposure period: not specified
Doses: 0, 0.67, 1.0, 2.0 %
Control Group: yes
NOAEL: = 400 mg/kg bw
LOAEL: = 800 mg/kg bw

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The NOAEL- and LOAEL-values given were calculated using the following parameters: NOAEL = 1% in diet, LOAEL = 2% in diet, 600 g diet/day, 15 kg body weight.
Result: It was concluded that diets containing 0.67, 1.0 and 2.0 % sodium lauryl sulfate for one year cause no anatomical abnormalities in dogs. For the group receiving 2 % SDS in their diet a decreased rate of body weight gain was observed.
Test substance: Sodium dodecyl sulfate USP (Duponol PC) from Dupont was tested.

(2) (3)

5.5 Genetic Toxicity 'in Vitro'

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Concentration: 5, 10, 20, 40, 80 ug per plate (without S-9-mix)
2.5, 10, 40, 160, 640 ug per plate (with S-9-mix).
Metabolic activation: with and without
Result: negative
Method: OECD Guide-line 471
Year: 1983
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Remark: First toxic effects were observed at a concentration of 200 ug per plate.
Test substance: Texapon K 12

(79) (88)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Metabolic activation: with and without
Result: negative

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

(15)

Type: Ames test
System of testing: Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Metabolic activation: with and without
Result: negative

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

(170)

Type: Ames test
System of testing: Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration: Half-log doses up to a dose that elicited toxicity
Metabolic activation: with and without
Result: negative

Method: other: according to Haworth et al.
Year: 1983
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Test substance: Sodium dodecylsulfate of 98.4% purity from Alcolac, Inc. was tested.

(66) (117)

Type: other: Gene mutation assay with filamentous fungi
System of testing: Heterozygous dipoloid strain of Aspergillus nidulans
Concentration: 0, 0.03, 0.06, 0.09, 0.12 %
Metabolic activation: without
Result: negative

Method: other: according to Ref. Assinder et al. (1985)
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Both the toxicity and the genetic activity were investigated, the latter being assessed from the frequency of abnormal, aneuploid colonies.
Test substance: Sodium dodecylsulfate from Sigma Chemicals Ltd. was used.

(9)

Type: Mouse lymphoma assay
System of testing: L5178Y tk+/- mouse lymphoma cell forward mutation assay
Concentration: 10, 20, 20, 40, 50, 60, 70 ug/ml
Metabolic activation: with and without
Result: negative

Method: other: according to Ref. Clive et al.
Year: 1979
GLP: no data
Test substance: no data

Remark: The test substance was supplied under a code number from the National Toxicology Program Chemical Repository, Radian Corporation, Austin, USA. No quality stated.
(43) (112)

5.6 Genetic Toxicity 'in Vivo'

Type: Micronucleus assay
Species: rat Sex: male/female
Strain: no data
Route of admin.: oral feed
Exposure period: 90 days access to food ad libitum
Doses: 0.0, 0.56, 1.13 %
Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: The results showed that feeding rats 0.56 and 1.13 % sodium lauryl sulfate in the diet for 90 days produced no increase in chromosomal aberrations nor did the chemical cause a clastogenic effect.
Test substance: Sodium lauryl sulfate 99% purity from BDH was tested.
(90)

5.7 Carcinogenicity

Species: dog Sex: male/female
Strain: Beagle
Route of administration: oral feed
Exposure period: 1 year
Frequency of treatment: permanent access to food ad libitum
Post exposure period: not specified
Doses: up to 2 %
Control Group: yes

Method: other: not specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: The administration of test compound at concentrations up to 2 % wasn't tumorigenic or carcinogenic to beagles.
(47)

5.8.1 Toxicity to Fertility

Type: Fertility
Species: mouse
Sex: male
Strain: Swiss
Route of administration: oral feed
Exposure Period: two weeks (for dose 1%), six weeks (for dose 0.1%)
Frequency of treatment: continuous

Premating Exposure Period
male: two weeks (for dose 1%), six weeks (for dose 0.1%)
female: none
Duration of test: fife weeks (for dose 1%), nine weeks (for dose 0.1%)
Doses: 0.1 %, 1.0%
Control Group: yes
Method: other: described by Hemsworth (1981)
GLP: no data
Test substance: no data

Result: Male mice exposed either to 0.1% SDS for six weeks or to 1.0% SDS for two weeks produced litters of normal size. In a repeat experiment at the 1.0%, again no adverse effect on male fertility was observed. The incidence of prenatal mortility did not differ significantly from the control level. The animals maintained at the 1.0% level incurred a significant reduction in body weight.

The author concludes that, although SDS is a powerful spermicidal detergent on the basis of its activity in-vitro, it is inactive in this context when given to male mouse by the oral route. SDS had no antifertility action referable to impairment of epididymal spermatozoa when administered in a concentration sufficient to cause a significant reduction in body weight.

Test substance: Sodium dodecylsulfate of unstated quality was tested.
(68)

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: other: CD
Route of administration: gavage
Exposure period: from day 6 to day 15 of gravidy
Frequency of treatment: daily
Doses: 0.0, 0.2, 2.0, 300.0, 600.0 mg/kg
Control Group: yes
NOAEL Maternal Toxity: < 300 mg/kg bw
NOAEL Teratogenicity: = 600 mg/kg bw

Method: other: described in Ref. Palmer et al. (1975)
GLP: no data
Test substance: no data

Result: Slight to moderate maternal toxicity was observed in animals receiving 300 and 600 mg/kg. There were no effects of fetal morphogenesis.
Test substance: Tested substance was "alcohol sulfate" (quality and chain length not stated, probably technical grade sodium lauryl sulfate), supplied by Lion Fat & Oil Co. Ltd., Japan.
(122)

Species: mouse Sex: female
Strain: CD-1
Route of administration: gavage
Exposure period: from day 6 to day 15 of gravidy
Frequency of treatment: daily
Doses: 0.0, 0.2, 2.0, 300.0, 600.0 mg/kg
Control Group: yes

NOAEL Maternal Toxity: < 300 mg/kg bw
NOAEL Teratogenicity: = 300 mg/kg bw

Method: other: described in Ref. Palmer et al. (1975)
GLP: no data
Test substance: no data

Result: Slight to moderate maternal toxicity was observed in mice receiving 300 mg/kg. Marked maternal toxicity in the form of anorexia, death, and abortion (and/or total resorption) was evident only in animals dosed with 600 mg/kg. No effects on fetal morphogenesis were observed in any dose.
Test substance: Tested substance was "alcohol sulfate" (quality and chain length not stated, probably technical grade sodium lauryl sulfate), supplied by Lion Fat & Oil Co. Ltd., Japan.
(122)

Species: rabbit Sex: female
Strain: other: New Zealand
Route of administration: gavage
Exposure period: from da 6 to day 18 of gravidy
Frequency of treatment: daily
Doses: 0.0, 0.2, 2.0, 300.0, 600.0 mg/kg
Control Group: yes
NOAEL Maternal Toxity: < 300 mg/kg bw
NOAEL Teratogenicity: = 300 mg/kg bw

Method: other: described in Ref. Palmer et al. (1975)
GLP: no data
Test substance: no data

Result: Slight to moderate maternal toxicity was observed in rabbits receiving 300 mg/kg. Marked maternal toxicity in the form of anorexia, death, and abortion (and/or total resorption) was evident only in rabbits dosed with 600 mg/kg. No effects on fetal morphogenesis were observed in any dose.
Test substance: Tested substance was "alcohol sulfate" (quality and chain length not stated, probably technical grade sodium lauryl sulfate), supplied by Lion Fat & Oil Co. Ltd., Japan.
(122)

Species: mouse Sex: female
Strain: ICL-ICR
Route of administration: dermal
Exposure period: from day 6 to day 13 of gravidy
Frequency of treatment: daily
Doses: 0.0, 0.4, 4.0, 6.0 %
Control Group: yes

Method: other: not specified
GLP: no data
Test substance: no data

Remark: A NOAEL-value in mg/kg/day could not be calculated, due to lack of experimental details given. The test was not done in accordance to established EEC or OECD-protocols nor to GLP. The result is ambiguous.

Result: Sodium lauryl sulfate (4.0 and 6.0) % applied topically to pregnant mice caused cleft palate and delayed bone

ossification in some offsprings. The authors stated that the occurence of these anomalies in test and control mice may or may not be significant.

Test substance: Sodium lauryl sulfate of unspecified origin and purity.
(147)

5.8.3 Toxicity to Reproduction, Other Studies

-

5.9 Specific Investigations

-

5.10 Exposure Experience

Remark: To evaluate the dermatological safety of sodiumlaurylsulfate, the substance was tested at various concentrations between 0.1 and 10% on test persons. The irritation potential was directly related to the concentrations applied. An upper limit of 1% was recommended for non-rinse-off products.
(46)

Remark: 50 % sodiumlaurylsulfate solution (0.5 ml) was applied on the skin of six test persons. After 4, 24 and 48 h scores were given for erythema and edema on a 0-4 scale. Result: sodiumlaurylsulfate is only slightly irritating to the human skin.
(120)

5.11 Additional Remarks

Type: Neurotoxicity

Remark: The effect of sodium dodecyl sulfate (SDS) an anionic amphiphilic detergent, on the function of human neutrophils and the human promyelocytic leukemia cell line HL-60 was investigated. SDS modulated the respiratory burst in human neutrophils and HL-60 cells which were stimulated with phorbol 12-myristate 13-acetate (PMA). In concentrations above 1 x 10-6 M it also caused release of lysosomal enzymes (beta-D-glucuronidase, myeloperoxidase and lysozyme) from neutrophils. The results demonstrate that SDS at concentrations 1 x 10-6 to 1 x 10-4 M strongly affect properties of human phagocytic cells. From the results in the article the authors conclude that SDS in concentrations above 1 x 10-4 M can damage important metabolic functions of neutrophils, whereas in concentrations of 1 x 10-4 to 1 x 10-6 M SDS stimulates enzymatic activities. The chronic stimulatory effect of low SDS concentrations present in various cleaning and washing detergents on respiratory burst of professional phagocytes may disturb their activation capacity and thus lead to an imbalance of immune homeostasis. Although this study does not deal with the determination of SDS concentrations in the environment, it is possible to estimate the potential risk associated with the widespread and commercial use of SDS and allied compounds. Daily use of washing and cleaning

preparations may cause chronical exposure in concentration ranges which were tested in this study. Briefly, by the common use of tooth-paste, the oral mucous membrane is exposed to SDS concentrations of more than 10-4 M (calculated from composition of commercial products). At present there is a lack of well-documented correlations in this field, and further investigations need to be performed.

(94)

Type: other: Hautverträglichkeit an exzisierter Mäusehaut

(81)

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Attachment 6

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

June 4, 2009

MEMORANDUM

SUBJECT: Summary of Product Chemistry, Environmental Fate, and Ecotoxicity Data for Silver, Silver Salts, Silver Zeolites (Copper and Zinc) and Silver Sodium Hydrogen Zirconium Phosphate For Registration Review

RR Case Name	PC Codes	CAS #
Silver	072501	7440-22-4
Silver sulfate	072511	10294-26-5
Silver nitrate	072503	7761-88-8
Silver chloride	072506	7783-90-6
Silver oxide	129097	155645-89-9
Silver/Na/H/Zr Phosphate	072560	265647-11-8
Silver Zeolite	221700	130328-19-7

RR Case No.: 4082 and 5015

FROM: A. Najm Shamim, PhD, Chemist
Regulatory Management Branch II
Antimicrobials Division (7510P)

A Shamim 6/15/09

TO: Heather Garvie, CRM for Silver Registration Review
Regulatory Management Branch II
Antimicrobials Division (7510P)
and
Mark Hartman, Chief
Regulatory Management Branch II
Antimicrobials Division (7510P)

THRU: Norman Cook, Branch Chief
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510P)

Attached is the summary of available product chemistry, environmental fate, and ecotoxicity data to support the registration review of silver and compounds.

SILVER AND COMPOUNDS: ENVIRONMENTAL AND ECO-EFFECTS SCOPING DOCUMENTS

TABLE OF CONTENTS PAGE No.

Important Notes: The registration review is unique in more than one way from regulatory as well as from science perspective:

1. From regulatory perspective, it contains chemicals which are registered under two different Case Numbers: 4082, and 5015. For the present work, the Agency has decided to keep the two Case Numbers separate, and merging of the two cases into will be decided later
2. Two distinct classes of chemicals are reviewed in this document: 1) Silver (elemental) and silver salts and 2) Silver (copper and or zinc) zeolites as well as Silver Sodium Hydrogen Zirconium Phosphate.
3. Physical and chemical characteristics of these differ from each other, and this is particularly noticeable in regards to their solubilities in water. a synopsis of the solubilities is as follows:

Chemical	**Solubility**
Metallic Silver	~ 0.0
Silver Nitrate	~ 200 g/100ml
Silver Sulfate	1.2 g/100ml
Silver Oxide	0.0013 g/100 ml
Silver Zeolites	< 10 µg/L
Silver Na/H/Zr Phosphate	0.000026 g/100 ml

4. Because all of them contain silver at the core, the Agency will take into account the speciation of silver in various environmental media like water, soils and sediments, fish and mammals.

5. As silver and silver salts are being considered together for risks, and silver zeolites and silver hydrogen sodium zirconium phosphate separately, the use patterns/uses are summarized in the following table:

Chemical name(s)	**Use patterns/use sites**
Silver and Silver Salts	Agricultural and farm premises, egg grading and product establishments, mushroom farm premises, material preservative, adhesives and sealants, textile fiber, paper coating, coating films, paints, dyes, pigments, drinking water, contact surfaces, humidfiers, hard non-porous surfaces, transportation, medical premises, dental unit water lines processing wash water, water purification units, swimming pools, spas, plastics, coatings, films, and laminates
Silver Zeolites (copper and zinc)	Fibers, conveyer belts, apparels, plastic films, and molded plastics, paper coatings, paints, adhesives, water purification units,
Silver Na/H/Zr-Phosphate	Material preservatives, plastic vinyl PVC products, adhesives, sealants, fibers, conveyer belts, coatings, films, upgrade coatings, HVAC, sinks, plaster, shingles, roofing, sidings

SILVER
REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 072501; Case No. 4082

Introduction:

The Antimicrobials Division (AD) Registration Review Team has evaluated the status of the environmental fate and ecological assessments for silver, silver salts, and silver zeolites . Included in this registration review are two cases: Case 4082, which includes silver salts [silver (072501), silver nitrate (072503), silver chloride (072506), silver sulfate (072511), silver oxide (129097), and silver zeolites (221700]; and Case 5015, silver sodium zirconium hydrogen phosphate (072560). For purposes of environmental fate and ecological assessment, AD considered that silver and silver salts could be considered together, while silver zeolite represented a different class and was not included with silver salts. Therefore, environmental fate and ecological databases are separate for silver and silver salts and for silver zeolite.

Registrations exist within the Antimicrobials Division (AD) of the Office of Pesticide Programs (OPP) for several types of silver-based pesticidal active ingredients, including registrations or proposed registrations for metallic silver, silver salts (such as silver nitrate, silver chloride, etc.), zeolite-based silver compounds (such as silver-copper zeolite, silver-zinc zeolite, etc.), powdered glass matrices such as silver-boron silica phosphate, and silver mixtures such as silver + citric acid. Antmicrobial use sites for silver include medical premises and equipment, human drinking water systems, materials preservatives, and swimming pools. For silver nitrate, use sites include drinking water filters and swimming pools. For silver chloride, use sites include fibers and textiles and swimming pools. Silver oxide use sites include spas, hot tubs, whirlpools, and pools. Silver sodium hydrogen zirconium phosphate and other silver zeolites have uses as a materials preservative in plastic film, paint, paper coatings, adhesives, synthetic fibers, pigments, and textile finishing and manufacturing. Indirect food contact uses are also included.

Silver was first registered for use as a pesticide in the United States in 1960 to inhibit the growth of bacteria in filters used in human drinking water systems. There are currently 93 active products and four (4) pending products. There are no inert uses for this chemical.

Silver - PC Code: 072501

Table 1: Registered Active Products of Silver (elemental)
[4082 Silver Compounds: PC code 072501-Silver]

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
707-313	SilvaDur™	Soluble Concentrate	2.95	Rohm and Haas Company
7124-101	nu-clo Silvercide	Ready-to-Use Solution	0.8	Alden Leeds Inc
10324-18	ALGAESIL	Ready-to-Use Solution	0.8	Mason Chemical Company
11631-5	Antimicrobial AlphaSan® CW 12	Dust	1.8	Milliken Chemical
35900-2	HYGENE®	Granular	1.05	Puronics Water Systems, Inc.
35900-3	General Ionics Model IQ0820B Bacteriostatic Water Conditioner with HYGENE®	Impregnated Materials	0.07	Ionics, Incorporated
35900-9	General Ionics Model IQ 1240B Bacteriostatic Water Conditioner with HYGENE®	Impregnated Materials	0.07	Ionics, Incorporated
35900-18	General Ionics Model 200,000 Bacteriostatic House Water Filter	Impregnated Materials	0.35	Ionics, Incorporated
35900-19	General Ionics Model IQ 1030B Bacteriostatic Water Conditioner	Impregnated Materials	0.07	Ionics, Incorporated
37589-2	X-262 Bacteriostatic Silver Impregnated Activated Carbon	Impregnated Materials	0.2	BESTECH, INC.
37589-4	X-462 Bacteriostatic Silver Impregnated Activated Carbon	Impregnated Materials	1.05	BESTECH, INC.
37589-5	Mariner Renaturalizer Water Unit Processor	Impregnated Materials	0.75	BESTECH, INC.
39104-1	AQUACELL Bacteriostatic Water Treatment Unit	Impregnated Materials	1.05	Kabb, Inc.
39444-8	Micropur® MFL	Soluble Concentrate	0.08	Katadyn, U.S.A., Inc.
39444-9	Micropur® MP	Wettable Powder	1	Katadyn, U.S.A., Inc.
40810-23	IRGAGUARD® B102 N Silver-Zinc glass	Formulation Intermediate	0.41	CIBA Specialty Chemicals Corp.
40810-24	IRGAGUARD® B7000 Silver-Zinc Glass	Dust	0.37	CIBA Corporation
40810-26	IRGAGUARD® B102 M Silver-glass	Formulation Intermediate	1.57	CIBA Specialty Chemicals Corp.
42177-76	REGAL SILVER ALGAECIDE	Ready-to-Use Solution	0.8	Alliance Trading, Inc.

44751-1	NSA BACTERIOSTATIC WATER TREATMENT UNIT, MODEL 50C	Impregnated Materials	0.105	National Safety Associates, Inc.
44751-3	NSA BACTERIOSTATIC WATER TREATMENT UNIT, MODEL 251	Impregnated Materials	0.117	National Safety Associates, Inc.
44751-4	NSA BACTERIOSTATIC WATER TREATMENT UNIT, MODEL 300H	Impregnated Materials	0.075	National Safety Associates, Inc.
44751-5	Mini-Silverator Portable Water Treatment Unit	Impregnated Materials	0.624	National Safety Associates, Inc.
44751-7	Mini-Silverator Recharge Water Treatment Media	Impregnated Materials	0.624	National Safety Associates, Inc.
54625-2	BRITA® Water Filter Travel Pak	Impregnated Materials (filter cartridge)	0.016	The BRITA Products Company
57787-21	Silver Algaecide	Ready-to-Use Solution	0.8	Haviland® Consumer Products, Inc.
58295-1	BARNEBEY & SUTCLIFFE TYPE 989 BACTERIOSTATIC WATER FILTER MEDIA	Impregnated Materials	0.026	Barnebey & Sutcliffe Corporation
58295-2	BARNEBEY & SUTCLIFFE TYPE CE BACTERIOSTATIC WATER FILTER MEDIA	Impregnated Materials	1.05	Barnebey & Sutcliffe Corporation
58295-3	BARNEBEY & SUTCLIFFE TYPE 1184 BACTERIOSTATIC WATER FILTER MEDIA	Impregnated Materials	0.5	Barnebey & Sutcliffe Corporation
62275-1	EUROCARB Bacteriostatic Water Filter Media	Impregnated Materials	0.07	Eurocarb Products, Ltd.
67619-18	Silvio	Soluble Concentrate	0.003	Clorox Professional Products Company
67712-1	Nature^{2}® G45-VC40	Impregnated Materials (cartridge)	3.51	Zodiac Pool Care, Inc.
67712-5	Nature^{2}® AG	Impregnated Materials (cartridge)	2.33	Zodiac Pool Care, Inc.
67712-15	Nature^{2} Spa	Impregnated Materials (cartridge)	0.92	Zodiac Pool Care, Inc.
68161-1	Silver Algaedyn®	Ready-to-Use Solution	0.8	Pool Products Packaging Corporation
68317-1	APACIDER-AK	Dust/Powder	1.5	Sangi America
68317-2	APACIDER-AW	Dust/Powder	2.03	Sangi Company, Ltd.
68317-4	APACIDER-AK (For WATER FILTERS/MEDIA)	Impregnated Materials	1.5	Sangi Company, Ltd.
68934-1	Aqua Select Water Filter	Impregnated Materials (cartridge)	0.0011	Aqua Select U.S.A., Ltd.

69096-3	BIOTECT	Technical Chemical (metallic silver)	99.51	Fairey Industrial Ceramics, Ltd.
70404-9	TINOSAN® SDC-R	Formulation Intermediary	0.24	CIBA Specialty Chemicals
70404-10	HyGate™ 4000	Formulation Unidentified	100	CIBA Corporation
70927-1	X-Static®-XS	Impregnated Materials (silver coated nylon fiber)	17	Noble Fiber Technologies, LLC.
70927-2	X-Static®-XF	Soluble Concentrate (silver coated nylon fiber)	15	Noble Fiber Technologies, LLC.
70927-3	X-Static®-XN	Soluble Concentrate (silver coated nylon fiber)	9	Noble Fiber Technologies, LLC.
70927-4	X-Static®-XT	Soluble Concentrate (silver coated nylon fiber)	13	Noble Fiber Technologies, LLC.
70927-5	X-Static®-XW	Impregnated Materials (silver coated nylon fiber)	20	Noble Fiber Technologies, LLC.
71272-1	Technical Silver	Technical Chemical (MUP)	99.98	Austech PTY, Ltd.
71332-5	EPL 0.25 Silver/Ceramic Filter Material	Impregnated Materials	0.25	Envirogard Products, Ltd.
71661-1	SURFACINE® ALL PURPOSE CLEANER	Ready-to-Use Solution	0.0095	Intelligent Biocides LLC
72854-1	AgION® Silver Antimicrobial Type AD	Ready-to-Use Solution	22	AgION Technologies, Inc.
72854-2	AgION® Silver Antimicrobial Type AL	Ready-to-Use Solution	10	AgION Technologies, Inc.
72977-1	AXENOHL®	Formulated Intermediate	0.24	ETI H_2O, Inc.
72977-2	AXEN®	Ready-to-Use Solution	0.0012	ETI H_2O, Inc.
72977-3	Axen® 30	Ready-to-Use Solution	0.003	ETI H_2O, Inc.
72977-5	SDC3A	Ready-to-Use Solution	0.003	ETI H_2O, Inc.
73148-1	IONPURE WPA (Silver-Glass)	Dust	1.6	Ishizuka Glass Co., Ltd.
73148-2	IONPURE ZAF (Silver-Glass)	Wettable Powder/Dust	0.42	Ishizuka Glass Co., Ltd.
73148-3	IONPURE ILP (Silver-Glass)	Dust	1.8	Ishizuka Glass Co., Ltd.
73148-4	IONPURE IPM (Silver Glass)	Formulation Intermediate	2.5	Ishizuka Glass Co., Ltd.
73148-5	IONPURE IZA (Silver Glass)	Formulation Intermediate	2.6	Ishizuka Glass Co., Ltd.
73148-6	IONPURE ZAF HS (Silver-Glass)	Dust	1.8	Ishizuka Glass Co., LTD.
73148-7	IONPURE ZAF MS (Silver-Glass)	Wettable Powder/Dust	0.9	Ishizuka Glass Co., LTD.
73499-1	ASAP-AGX	Ready-to-Use	0.001	American Silver,

		Solution		LLC
73499-2	ASAP-AGX-32	Ready-to-Use Solution	0.0032	American Biotechs, LLC
73667-5	MB 2200 G	Formulation Intermediate	1.4	Apyron Technologies, Inc.
73667-6	MB 2001 G	Granular	0.7	Apyron Technologies, Inc.
73667-7	MB 2001XG	Formulation Intermediate	0.63	Apyron Technologies, Inc.
74627-5	Zeocide AG	Dust	3.5	Product & Regulatory Associates, L.L.C.
74802-2	BACTERIOSTATIC WATER CONDITIONER MODEL AM1054AG	Impregnated Materials	1.05	Aqua Maid Water Systems, Inc.
75456-1	AquaSorb® LS 0.05 Ag	Impregnated Materials	0.05	Jacobi Carbons, Inc.
75829-1	H_2Pro^{TM} Maintenance Treatment	Soluble Concentrate	0.0015	Garrison Dental Solutions
79630-1	AQUASTAT HU	Impregnated Materials (cartridge)	1.4	K2 Concepts, Inc.
79630-2	AQUASTAT® -XR	Formulation Intermediate	1.4	K2 Concepts, Inc.
82415-1	BACTEKILLER AC	Dust	3.5	Fugi Chemical Industries, LTD.
82415-8	BACTEKILLER G Silver-Glass	Dust	1.8	Fugi Chemical Industries, LTD.
82691-2	STAY CLEAN ADDITIVE B	Ready-to-Use Solution	100	American Standard Companies, Inc.
83587-3	ADDITIVE SSB	Soluble Concentrate	99.9	Nanohorizons, Inc.
84020-1	BluTab™ Waterline Maintenance	Pelleted/Tableted	0.447	Confirm Monitoring Systems, Inc.
84054-1	Konica Nice Print System Cleaning Agent-J	Impregnated Materials	1.05	Allied Diagnostic Imaging Resources, Inc.
84146-1	MicroSilver BG-R	Technical Chemical	100	Bio-Gate AG
84214-1	ProTex^{AG} Fiber	Impregnated Materials	17	CAROLINA SILVER, LLC
84526-1	Sanosil® S010	Ready-to-Use Solution	0.01	Greenhouse International, LLC

Chemical Identity

Table 2. Chemical Identity

Common Name	Silver
Chemical Name	Silver
IUPAC	Silver
Molecular Weight	107.8682
PC Code	072501
CAS Registry Number	7440-22-4
Empirical Formula	Ag
Registration Review Case No.	4082
Registration Review Case Name	Silver and compounds
Classification:	Inorganic
Chemical Symbol:	Ag

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver. The findings are summarized below:

Science Findings:

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver are considered incomplete.

Table 3. Physical and Chemical Properties of Silver

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	*
830.1620	Description of production process	*
830.1650	Description of formulation process	*
830.1670	Discussion of formation of impurities	*
830.1700	Preliminary analysis	*
830.1750	Certified limits	*
830.1800	Enforcement analytical method	*
830.1900	Submittal of samples	*
830.6302	Color	Metallic[1]
830.6303	Physical State	Solid[1]
830.6304	Odor	None[1]
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable to sunlight and metal/metal ions[1]

Guideline No.	Physical and Chemical Properties	Value
830.6314	Oxidation/Reduction: Chemical Incompatibility	*
830.6315	Flammability Flash Point	*
830.6316	Explodability	*
830.6317	Storage Stability	*
830.6319	Miscibility	*
830.6320	Corrosion Characteristic	*
830.6321	Dielectric breakdown voltage	*
830.7000	pH	NA[1]
830.7050	UV/Visible absorption	NA
830.7100	Viscosity	NA[1]
830.7200	Melting Point	960.5 °C[1]
830.7220	Boiling point	2000 °C[1]
830.7300	Density	10.49 g/ml @ 15 °C[1]
830.7370	Dissociation Constants in water	NA[1]
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{OW})	NA
830.7840	Solubility in water	Insoluble in water[1]
830-7840	Solubility in organic solvents in g/100 ml	*
830.7950	Vapor pressure	100 mmHg @ 1, 865 °C for liquid silver[2]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

* Data not submitted. The Agency anticipates that it will need these data for this chemical.

Environmental Fate Data Summary

No environmental fate studies for elemental silver have been submitted. Agency considers the current environmental fate guidelines studies to be inadequate for fate studies. The current environmental fate guidelines are tailored for organics and do not address the metals. The Agency is proposing an alternate approach as outlined later in the document. Only following two studies are need.

Environmental Fate Data Gaps:

- (GLN 850.6800) modified activated sludge respiration inhibition;
- (GLN 835.1110) activated sludge sorption isotherm

Ecotoxicity Summary

The Agency has an adequate ecological toxicity data base for silver and silver salts. Therefore, these data are adequate for assessing risk from potential ecological exposures to elemental silver and silver salts.

SILVER SULFATE
REGISTRATION REVIEW DECISION
PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 072511; Case No. 4082

Introduction:

Silver sulfate was first registered for use as a pesticide in the United States in 2006 for use as a material preservative to be incorporation during the manufacturing process. There is currently one active product containing silver sulfate, no pending products and no inert uses for this chemical.

The current active product is a material preservative for incorporation into apparel, plastic, paper coatings, paints, adhesives, film and molded plastics.

Table 1

Case 4082 Silver Compounds Appendix A PC code 072511 (Silver Sulfate)

Table 1. Registered Active Products of Silver Sulfate

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
59441	AGAM 100	Dust	98.5	Eastman Kodak Company

Table 2: Silver Sulfate

Table 2. Chemical Identity	
Common Name	Silver Sulfate
Chemical Name	Silver Sulfate
IUPAC	Silver Sulfate
Molecular Weight	311.80
PC Code	072511
CAS Registry Number	10294-26-5
Molecular Formula	Ag_2SO_4
Registration Review Case No.	4082
Registration Review Case Name	Silver and compounds
Classification:	Inorganic
Chemical Structure:	Ag^+ SO_4^{-2} Ag^+

Product Chemistry Summary of Silver Sulfate

Table 3. Physical and Chemical Properties of Silver Sulfate

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	CBI
830.1620	Description of production process	CBI
830.1650	Description of formulation process	CBI
830.1670	Discussion of formation of impurities	CBI
830.1700	Preliminary analysis	CBI
830.1750	Certified limits	CBI
830.1800	Enforcement analytical method	The Agency anticipates it will need this data
830.1900	Submittal of samples	NA
830.6302	Color	White[1]
830.6303	Physical State	Solid[1] at room temperature
830.6304	Odor	None[1]
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable to normal and elevated temperatures. Stable to metals
830.6314	Oxidation/Reduction: Chemical Incompatibility	Silver sulfate will react with organic reducing agents such as aldehydes and hydroxylamines
830.6315	Flammability Flash Point	NA: Material is a solid
830.6316	Explodability	Solid silver sulfate is known to be non-explosive
830.6317	Storage Stability	Stable
830.6319	Miscibility	NA
830.6320	Corrosion Characteristic	Not corrosive to plastic containers
830.6321	Dielectric breakdown voltage	NA: material is not for use around electrical equipment
830.7000	pH	NA[1]
830.7050	UV/Visible absorption	NA
830.7100	Viscosity	NA[1]
830.7200	Melting Point	652 °C[1]
830.7220	Boiling point	NA
830.7300	Density	5.56 g/ml
830.7370	Dissociation Constants in water	1.5×10^{-5}
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{OW})	NA
830.7840	Solubility in water	1.2 g/100ml at 20 ^{0} C
830-xxxx	Solubility in organic solvents in g/100 ml	*
830.7950	Vapor pressure	NA

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

- No Data Submitted. The Agency anticipates that it will need these data for the chemical.

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver sulfate. The findings are summarized below.

Product chemistry Data Summary

The product chemistry data for silver sulfate is deficient and the Agency anticipates that it will need these data as noted above.

Environmental Fate Summary

No environmental fate studies have been submitted and none have been reviewed. Agency considers the current environmental fate guidelines studies to be inadequate for fate studies. The Agency is proposing an alternate approach as outlined later in the document. Only following two studies are needed.

Environmental Fate Data Gaps:

- (GLN 850.6800) modified activated sludge respiration inhibition;
- (GLN 835.1110) activated sludge sorption isotherm

Ecotoxicity Summary

The Agency has no submitted ecotoxicity data for silver sulfate. However, the Agency has an adequate ecological toxicity data base for silver and silver salts. Therefore, these data are adequate for assessing risk from potential ecological exposures to elemental silver and silver salts.

SILVER NITRATE

REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 072503; Case No. 4082

Introduction:

Silver nitrate was first registered for use as a pesticide in the United States in 1973 for use as a fungicide and bacteriocide in pulp and paper mills. There are currently three active products and one pending product. There are no inert uses for this chemical.

The current active products for this chemical are used in the disinfection of swimming pools and the cleaning of dental line water as well as in the manufacturing of bacteriostatic water filters for treating municipally treated drinking water.

Table 1 4082 Silver Compounds Appendix A PC code 072503-Silver Nitrate

Table 1. Registered Active Products of Silver nitrate

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
5185-498	BioGuard® Crystal Blue Mineral Cartridge	Impregnated Materials (cartridge)	63.5	Bio-Lab, Inc.
69625-2	Silver Nitrate	Impregnated Materials	1.72	KX Industries L.P.
72992-1	Chrysal AVB	Soluble Concentrate	2.83	Pokon & Chrysal USA
79662-1	ICX®	Pelleted/Tableted	0.14	A-dec, Inc.

Chemical Identity

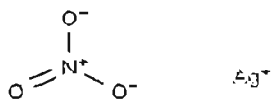
Table 2. Chemical Identity	
Common Name	Silver nitrate
Chemical Name	Silver nitrate, nitric acid silver (salt), silver (I) nitrate, silver mononitrate, silver (1+) nitrate
Molecular Weight	169.874
PC Code	072503
CAS Registry Number	7761-88-8
Molecular Formula	$AgNO_3$
Registration Review Case No.	4082
Registration Review Case Name	Silver and Compounds
Classification:	

Table 3. Physical and Chemical Properties on T.G.A.I of Silver Nitrate

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	*
830.1620	Description of production process	*
830.1650	Description of formulation process	CBI
830.1670	Discussion of formation of impurities	CBI
830.1700	Preliminary analysis	*
830.1750	Certified limits	CBI
830.1800	Enforcement analytical method	*
830.1900	Submittal of samples	*
830.6302	Color	Technical silver nitrate is colorless to white, and silver nitrate MUP is colorless.[1]
830.6303	Physical State	Technical silver nitrate is a solid crystalline, and silver nitrate MUP is a liquid.[1]
830.6304	Odor	Odorless[1]
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Technical silver nitrate is stable at room temperature. It discolors on exposure to light and decomposes into

Guideline No.	Physical and Chemical Properties	Value
		metallic silver, nitrogen, oxygen and nitrogen oxides when heated above 440°C.[1]
830.6314	Oxidation/Reduction: Chemical Incompatibility	Technical silver nitrate is a known oxidizer, and silver nitrate MUP can be considered an oxidizing agent.[1]
830.6315	Flammability Flash Point	The data requirement is not applicable since silver nitrate MUP does not contain any flammable components or combustible liquids.[1]
830.6316	Explodability	The data requirement is not applicable since silver nitrate MUP does not contain any explosive components and is not potentially explosive.[1]
830.6317	Storage Stability	A one-year storage stability study is currently being developed for silver nitrate MUP per the requirements of OPPTS 830.6317 and will be submitted to the Agency upon completion; conditional registration is requested with the requirement that this report provided to the Agency when complete.[1]
830.6319	Miscibility	This data requirement is not applicable since silver nitrate MUP is not emulsifiable liquid intended to be diluted with petroleum solvents.[1]
830.6320	Corrosion Characteristic	A corrosion characteristics study is currently being developed for silver nitrate MUP, in combination with the storage stability study, per the requirements of OPPTS 830.6320 and will be submitted to the Agency upon completion; conditional registration is requested with the requirement that this report be provided to the Agency when complete.[1]
830.6321	Dielectric breakdown voltage	This data requirement is not applicable since silver nitrate MUP is not intended for use around electrical equipment.[1] Waiver of this requirement is proposed. Silver chloride or products containing silver chloride will not be used around electrical equipment.[1]
830.7000	pH	The pH of technical silver nitrate is approximately 6.[1] Silver nitrate MUP has a pH of 7.81[1]
830.7050	UV/Visible absorption	The data requirement is not applicable since silver nitrate is not an organic compound.[1]
830.7100	Viscosity	Silver nitrate MUP has a viscosity of 0.99cP[2].[1]
830.7200	Melting Point	The melting point of technical silver nitrate is 212 °C.[1]
830.7220	Boiling point	Not applicable since technical silver nitrate is solid at ambient temperature.[1]
830.7300	Density	The density of technical silver nitrate is 4.5gm/cm^3. Silver nitrate MUP has a density of 1.0212 g/ml.[1]
830.7370	Dissociation Constants in water	The data requirement is not applicable since technical silver nitrate is salt which will dissociate upon aqueous dilution.[1]
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{ow})	The data requirement is not applicable since technical silver nitrate is an inorganic compound.[1]
830.7840	Solubility in water	Technical silver nitrate is soluble in water and glycerol and hot alcohol. It is slightly soluble ether.[1]

Guideline No.	Physical and Chemical Properties	Value
830-xxxx	Solubility in organic solvents in g/100 ml	
830.7950	Vapor pressure	The data requirement is not applicable since technical silver nitrate is an inorganic salt.[1]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

- No data submitted. The Agency anticipates it will need these data for this chemical.

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver nitrate. The findings are summarized below.

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver nitrate is deficient and the Agency anticipates it will these additional data for this chemical.

Environmental Fate Summary

No environmental fate studies have been submitted and none have been reviewed. The Agency considers the current environmental fate guidelines studies to be inadequate for fate studies. The Agency is proposing an alternate approach as outlined later in the document Only following two studies are needed.

Environmental Fate Data Gap:

(GLN 850.6800) modified activated sludge respiration inhibition;

(GLN 835.1110) activated sludge sorption isotherm

Ecotoxicity Summary

The Agency has ecotoxicity data in its database for silver nitrate. The data/results are summarized below in Table 4

Table 4. Ecological toxicity profile for silver nitrate

Guideline No. Test organism	Test Result	Test acceptability	MRID No.

850.1075 72-1a Bluegill	96-hr LC_{50} = 2.1 (1.5 – 3.0) mg/l	Supplemental	00054596
850.1075 72-1c Rainbow Trout	96-hr LC_{50} = 4.2 (3.8 – 4.7) mg/l	Supplemental	00054596
850.1010 72-2a Daphnia magna	48-hr LC50 = 0.19 (0.12 – 0.29) mg/l	Supplemental	00054596
Mallard duck	Oral LD50 > 4640 mg/kg	Supplemental	00054598
850.2100 71-1a Bobwhite quail	Oral LC50 > 1000 ppm	Supplemental	

Note: The Agency has an adequate ecological toxicity data base for silver and silver salts. Therefore, the data listed above and the data present in the Agency's database are adequate for assessing risk from potential ecological exposures to elemental silver and silver salts.

SILVER CHLORIDE

REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 072506; Case No. 4082

Introduction:

Silver chloride was first registered for use as a pesticide in the United States in 1976 for use as a filter in human drinking water systems. There are currently eight (8) active products and three pending registrations for this chemical. There no inert uses for this chemical.

The current active products for this chemical are used as part of a pool and spa disinfectant treatment system in addition to being used as a material preservative to be incorporated into fibers, textiles and apparel.

Table 1 4082 Silver Compounds Appendix A PC code 072506 Silver chloride

Table 1. Registered Active Products of Silver chloride

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
49403-34	JMAC Composite PG	Ready-to-Use Solution	20	Clariant Corporation
49403-36	JMAC™ LP10A	Ready-to-Use Solution	2	Clariant Corporation
53735-11	Pool Frog Mineral Reservoir	Impregnated Materials	0.5	King Technology Inc.
59441-6	LOK-8008	Soluble Concentrate	4	Eastman Kodak Company
59441-7	Silver Chloride Technical	Technical Chemical	99.6	Eastman Kodak Company
59441-9	Textile Finishing Additive AGPET08	Ready-to-Use Solution (MUP)®	4	Eastman Kodak Company

Chemical Identity

Table 2. Chemical Identity	
Common Name	Silver Chloride
Chemical Name	Silver Chloride
IUPAC	Silver Chloride
Molecular Weight	143.32 g/mol
PC Code	072506
CAS Registry Number	7783-90-6
Molecular Formula	AgCl
Registration Review Case No.	4082
Registration Review Case Name	Silver and Compounds
Classification:	Inorganic
Chemical Structure:	

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver chloride. The findings are summarized below.

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver chloride are **adequate.**

Table 3. Physical chemical properties for Silver Chloride

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	CBI
830.1620	Description of production process	CBI
830.1650	Description of formulation process	CBI

Guideline No.	Physical and Chemical Properties	Value
830.1670	Discussion of formation of impurities	CBI
830.1700	Preliminary analysis	CBI
830.1750	Certified limits	CBI
830.1800	Enforcement analytical method	Not applicable. The slurry containing Silver Chloride is only used in preparation of the formulated product, and is not sold by itself. An enforcement analytical method for the formulation is provided in MRID 45448801.[1]
830.1900	Submittal of samples	Samples of slurry containing Silver Chloride will be submitted, if requested, subject to production schedules. All slurry made at a particular time is used immediately in production of the formulation.[1]
830.6302	Color	Milky white.[2] Silver chloride is a white powder, which darkens slowly when exposed to light.[3]
830.6303	Physical State	Solid.[2] White powder, a crystalline solid.[3]
830.6304	Odor	Odorless[2,3]
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable to temperature. Because Ag will replace metals in containers it is corrosive to stainless steel. Will darken in color when exposed to light.[2]
830.6314	Oxidation/Reduction: Chemical Incompatibility	Based on known chemistry, silver chloride will react with organic reducing agents such as aldehydes and hydroxylamines.[3] Silver chloride is not compatible with alkali metals, aluminum, ammonia, hydrazine, acetylene, or hydrogen peroxide. Silver ions, present in silver chloride, are readily reduced to silver metal, which is relatively noble. Silver chloride is therefore a moderately strong oxidant.[3]
830.6315	Flammability Flash Point	Not required since TGAI is a solid material.[2] Silver chloride is not flammable.[3]
830.6316	Explodability	Not explosive.[2] Waiver of this requirement is proposed. Silver chloride contains no functional groups, such as nitro groups or nitrate ions that would confer explosive potential. Not considered to be an explosion hazard.[3]
830.6317	Storage Stability	Silver chloride is known to be stable.[2] Silver chloride is generally considered stable, as it is one naturally-occurring ore of silver, known as horn silver. Silver chloride very gradually decomposes to silver and chlorine.[3]
830.6319	Miscibility	Not applicable as the material is solid.[2] Waiver of this requirement is proposed. From the guideline, the purpose of the requirement is to determine whether a formulation or solution is suitable for application after dilution with oil or other non-polar solvents. No use of silver chloride involves such application, so the requirement is not applicable.[3]
830.6320	Corrosion Characteristic	Not corrosive to plastic container. Waiver of this requirement is proposed. Silver chloride is a solid material, only very slightly soluble in water, and when dissolved cannot affect the pH of the solution (see OPPTS Guideline 830.7000 — pH). Therefore the material cannot cause corrosion through low pH.

Guideline No.	Physical and Chemical Properties	Value
		In addition, silver chloride is known to be stable for decades, when stored in its original container, tightly sealed. Normally silver chloride is stored in glass or HDPE bottles.[3]
830.6321	Dielectric breakdown voltage	Not applicable, product is not for use on electrical equipment. Waiver of this requirement is proposed. Silver chloride or products containing silver chloride will not be used around electrical equipment.[2]
830.7000	pH	Not applicable as the material is solid.[2] Waiver of this property is proposed. Silver chloride has a low solubility in water (see below. When dissolved in water, silver chloride produces silver ions and chloride ions, neither of which can affect the pH of the medium.[3]
830.7050	UV/Visible absorption	Not applicable.[2] Waiver of this requirement is proposed, primarily because silver chloride is insoluble in common solvents in which absorbance can be measured. In addition, from the guideline, the purpose of the requirement is to identify wavelengths at which the test species is likely to undergo photochemical degradation. Silver chloride is already known to degrade very slowly in light, turning dark in color as the result of formation of elemental silver on the surfaces of particles of silver chloride. In the process elemental chlorine is lost. Degradation is somewhat faster in ultraviolet light, and in fact served as the basis of the discovery of the ultraviolet portion of the spectrum.[3]
830.7100	Viscosity	Not applicable.[2] Waiver of this requirement is proposed. From the guideline, data on viscosity is needed to gauge the penetration of a fluid compound into soil and thence into groundwater. Silver chloride is a solid under all foreseeable environmental conditions and therefore cannot penetrate the soil as a fluid.[3]
830.7200	Melting Point	455 °C [2,3]
830.7220	Boiling point	Not applicable as the material is solid. 1550 °C.[3]
830.7300	Density	5.56 g/ml [2,3]
830.7370	Dissociation Constants in water	Insolube.[2] Refer also to OPPTS Guideline 830.7000 – pH. When dissolved in water, silver chloride produces silver ions and chloride ions, neither of which can affect the pH of the medium. Therefore silver chloride has no dissociation constant, in the normal sense. Silver chloride is, however, sparingly soluble in water, and its solubility is controlled by the common ion effect. The solubility of silver chloride satisfies a solubility product, as follows: $K_{sp} = [Ag^+][Cl^-]$ where Ksp is the solubility product, and the square

Guideline No.	Physical and Chemical Properties	Value
		brackets signify the molar concentrations of silver ions and chloride ions, respectively. The numerical value of Ksp is 1.77×10^{-10}. In the absence of other sources of chloride ions, the molar solubility of silver chloride in water is $(1.77 \times 10^{-10})^{1/2} = 1.33 \times 10^{-5}$ M.[3]
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{OW})	Insoluble.[2] Waiver of this requirement is proposed. From the guideline, the requirement applies only to non-polar organics. Silver chloride is neither non-polar, nor organic.[3]
830.7840	Solubility in water	Insoluble.[2] At 25 °C the aqueous solubility of silver chloride is 1.93 mg/L.[3]
830-7840	Solubility in organic solvents in g/100 ml	NA
830.7950	Vapor pressure	Not applicable as the material is solid.[2] At 912 °C silver chloride has a vapor pressure of 1 torr. At ambient conditions its vapor pressure will be negligible.[3]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

Environmental Fate Summary

Some environmental fate studies have been submitted and are being reviewed. The Agency considers the current environmental fate guidelines studies to be inadequate for fate studies. The Agency is proposing an alternate approach as outlined later in the document. Only following two studies are needed.

Environmental Fate Data Gaps:

(GLN 850.6800) modified activated sludge respiration inhibition;

(GLN 835.1110) activated sludge sorption isotherm

Ecotoxicity Summary

AD has reviewed an avian acute oral toxicity study (Northern Bobwhite) submitted by Eastman Kodak Company, in support of its proposed product, Silver chloride Technical, EPA File Symbol 59441-T. See the "Status/Results of Submitted Silver chloride Ecological Effects Study – 09-28-05" below:

Status/Results of Submitted Silver chloride Ecological Effects Study

Study	Species	MRID	Status	Results[1]
Avian Acute Oral Toxicity Test Using 99.6% Silver chloride	Northern Bobwhite	46453301	Core	LD_{50} = >2250 mg/kg NOEL = 1350 mg/kg

AD concludes that the submitted Avian Acute Oral Toxicity Study is scientifically sound and fulfills the U.S. Environmental Protection Agency's Ecological Effects Data Requirements. published in the Office of Prevention, Pesticides and Toxic Substances (OPPTS) Guideline 850.2100. The 15-day LD_{50} value of >2250 mg/kg classified the silver chloride as practically non-toxic to Northern Bobwhite (*Colinus virginianus*) birds. The NOEL was 1350 mg/kg. The study can be classified as core for a technical grade active ingredient.

Labeling:

Labels of both Manufacturing-Use Product (Silver Chloride Technical, EPA File Symbol 59441-T) and End-Use Product (LOK-8008 Biocide, EPA File Symbol 59441-T) must comply with EPA's current pesticide labeling requirements.

Under the heading "ENVIRONMENTAL HAZARDS" the following National Pollutant Discharge Elimination System (NPDES) statement must be included on both MP and EP proposed labels:

"Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans or other waters unless in accordance with the requirements of a National Pollutant Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA."

On both MP and EP proposed labels, revise the statement "This pesticide is toxic to fish and wildlife" to read "This pesticide is toxic to fish and aquatic invertebrates."

Note: The Agency has an adequate ecological toxicity data base for silver and silver salts. Therefore, these data are adequate for assessing risk from potential ecological exposures to elemental silver and silver salts

SILVER OXIDE

REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 129097; Case No. 4082

Introduction:

Silver oxide was first registered for use as a pesticide in the United States in 1996 for use as part of a pool disinfectant treatment system. There are currently two active products containing silver oxide as an active ingredient. There is one pending product and no inert uses for this chemical.

The current active products for this chemical are used in the disinfection of pools and spas.

Table 1: 4082 Silver Compounds Appendix A PC code 129097-Silver oxide

Table 1. Registered Active Products of Silver Oxide

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
3432-64	Sildate	Ready-to-Use Solution	2	N. Jonas & Co., Inc.
3432-71	SilSpa Disinfectant	Ready-to-Use Solution	1	N. Jonas & Co., Inc.

Chemical Identity

Table 2. Chemical Identity	
Common Name	Silver Oxide
Chemical Name	Silver Oxide
IUPAC	Silver oxide
Molecular Weight	231.74
PC Code	129097
CAS Registry Number	20667-12-3 (Ag_2O)
Molecular Formula	Ag_2O
Registration Review Case No.	4082
Registration Review Case Name	Silver and Compounds
Classification:	Inorganic

Table 2. Chemical Identity	
Chemical Structure::	Silver oxide Ag^{+} Ag^{+} O^{-2}

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver oxide. The findings are summarized below.

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver oxide are deficient.

Table 3. Physical chemical properties of silver oxide

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	*
830.1620	Description of production process	*
830.1650	Description of formulation process	*
830.1670	Discussion of formation of impurities	*
830.1700	Preliminary analysis	*
830.1750	Certified limits	*
830.1800	Enforcement analytical method	*
830.1900	Submittal of samples	*
830.6302	Color	Charcoal gray[1]
830.6303	Physical State	Powder[1]
830.6304	Odor	NA
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable at 100 °C for 18 hours[1]
830.6314	Oxidation/Reduction: Chemical Incompatibility	*
830.6315	Flammability Flash Point	*
830.6316	Explodability	*
830.6317	Storage Stability	*
830.6319	Miscibility	*
830.6320	Corrosion Characteristic	*
830.6321	Dielectric breakdown voltage	*

Guideline No.	Physical and Chemical Properties	Value
830.7000	pH	*
830.7050	UV/Visible absorption	NA
830.7100	Viscosity	*
830.7200	Melting Point	*
830.7220	Boiling point	NA
830.7300	Density	7.483 g/cm3[1]
830.7370	Dissociation Constants in water	NA
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{OW})	NA
830.7840	Solubility in water	27 mg/1 L @ 25 °C[1]
830-xxxx	Solubility in organic solvents in g/100 ml	NA
830.7950	Vapor pressure	NA[1]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

- No data submitted. The Agency anticipates that it will need these additional data for these chemicals

Ecotoxicity and Environmental Fate Summary

Note: Some environmental fate studies have been submitted and have been reviewed. The Agency considers the current environmental fate guidelines studies to be inadequate for fate studies. The Agency is proposing an alternate approach as outlined later in the document.

A study on hydrolysis: Hydrolysis of Ag (I, III) oxide at pH values of 5, 7, 9, is totally unknown. Silver oxide in does not hydrolyze unless it is exposed to extreme electrical factors. These electrical factors cause redox hydrolysis and involve electron transfers in the crystal lattice, which will cause the oxide to ionize like a salt.

The basic hydrolytic redox reactions of Ag (I, III) with water and electrons produce metallic silver and hydroxide.

$$Ag_4O_4 + 2H_2O + 4e = 2Ag_2O + 4OH$$

$$Ag_2O_2 + H_2O + 2e = 2Ag + 2OH$$

These studies indicate the fact that alkaline solutions provide the basis for such reductive hydrolysis. Therefore, at lower pH without the reductive extreme pH (> 14), hydrolytic effects may not be noticed.

Only following two studies are needed for environmental and transport:

o GLN 850.6800) modified activated sludge respiration inhibition;

(GLN 835.1110) activated sludge sorption isotherm

No ecotoxicity data were submitted for this chemical; however, Agency's ecotoxicity data for silver and silver salts are sufficient to conduct the ecotoxicity assessment

SILVER ZEOLITE

REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY

PC Code: 221700; Case No. 4082

Introduction:

Silver zeolite was first registered for use as a pesticide in the United States in 1994 for use as a material preservative to be incorporation during the manufacturing process. There is currently one active product containing silver zeolite, no pending products and no inert uses for this chemical.

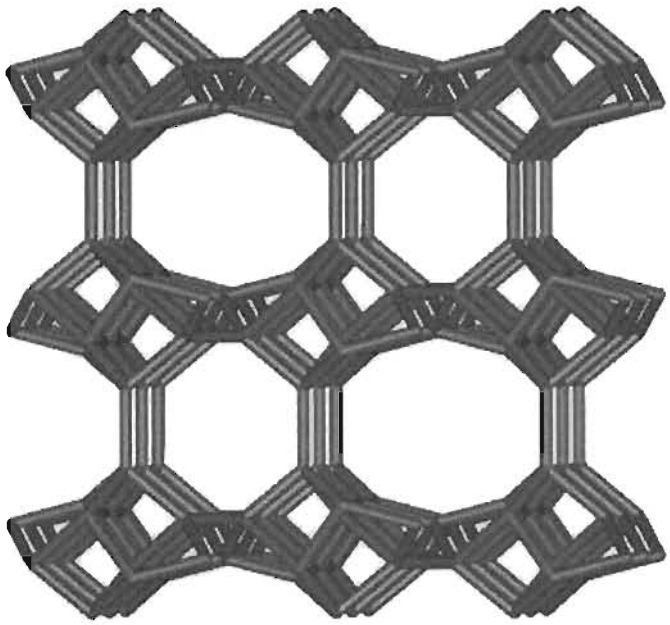
The current active product is a material preservative for incorporation into apparel, plastic, paper coatings, paints, adhesives, film and molded plastics.

Table 1 **Case 4082 Silver Compounds Appendix A PC code 221700 (Silver Zeolite)**

Table 1. Registered Active Products of Silver (copper) and silver (zinc) zeolite

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
82415-3	BACTEKILLER A	Wettable Powder/Dust	3.5	Fuji Chemical Industries, Ltd.
71227-1	Zeomic® Type AJ Silver Zeolite A	Soluble Concentrate	2.5	Sinanen Company, Ltd.
71227-4	Zeomic® Type AK Silver Zeolite A	Crystalline	4.93	Sinanen Company, Ltd.
71227-5	Zeomic® Type AW Silver Zeolite A	Soluble Concentrate	0.59	Sinanen Company, Ltd.
71227-6	Zeomic® Type AV Silver Zeolite A	Soluble Concentrate	0.3	Sinanen Company, Ltd.
71227-7	Zeomic® Type AC Silver Copper Zeolite A	Dust	3.5	AgION Technologies, Inc.
82415-2	BACTEKILLER® AZ (Silver-Zinc Zeolite)	Wettable Powder	6.5	Fugi Chemical Industries, LTD.
40810-18	IRGAGUARD ® B5000 Silver-Zinc Zeolite	Formulation Intermediate	0.44	CIBA Corporation
40810-19	IRGAGUARD ® B502 I Silver-Zinc Zeolite	Formulation Intermediate	2.2	CIBA Specialty Chemicals Corp.
40810-27	IRGAGUARD® B6000 Silver Glass-Zinc Zeolite	Soluble Concentrate	1.18	CIBA Corporation

Table 2

Table 2. Chemical Identity	
Common Name	Silver Zeolite (Copper and Zinc)
Chemical Name	Silver Zeolite
IUPAC/Other Names	Aluminum sodium silicate - silver complex/ Bactekiller A Zeolites, Ag
Formula Weight	Variable
PC Code	221700/ (Cu-zeolite); 129103 (Zn-zeolite)
CAS Registry Number	130328-18-6 (Cu- zeolite); 130328-20-0(Zn-zeolite)
Empirical Formula	Variable
Registration Review Case No.	4082 /5015
Registration Review Case Name	Silver and Compounds
Classification:	Inorganic
Chemical Structure::	Silver Zeolites Variable 

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver zeolite. The findings are summarized below.

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver zeolite are **adequate**

Table 3

Physical/Chemical Properties for Silver Zeolites (Copper and Zinc)

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	CBI
830.1620	Description of production process	CBI
830.1650	Description of formulation process	CBI
830.1670	Discussion of formation of impurities	CBI
830.1700	Preliminary analysis	CBI
830.1750	Certified limits	CBI
830.1800	Enforcement analytical method	Agency will need this data for its database
830.1900	Submittal of samples	NA
830.6302	Color	White
830.6303	Physical State	Solid Powder[1]
830.6304	Odor	Odorless
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Very Stable
830.6314	Oxidation/Reduction: Chemical Incompatibility	NA
830.6315	Flammability Flash Point	NA
830.6316	Explodability	NA
830.6317	Storage Stability	Material maintains stability during storage up to a year; no change in properties after one year
830.6319	Miscibility	NA
830.6320	Corrosion Characteristic	NA
830.6321	Dielectric breakdown voltage	NA
830.7000	pH	A slurry with water has a pH 0f 9.00
830.7050	UV/Visible absorption	NA
830.7100	Viscosity	NA
830.7200	Melting Point	> 2900 ° C
830.7220	Boiling point	NA
830.7300	Density	2.2 g/cm3[1]
830.7370	Dissociation Constants in water	NA
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{OW})	NA
830.7840	Solubility in water	Almost insoluble in water < 5 ppb in water
830-xxxx	Solubility in organic solvents in g/100 ml	Almost insoluble in alcohol, and non-polar solvents

Guideline No.	Physical and Chemical Properties	Value
830.7950	Vapor pressure	NA[1]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

Ecotoxicity and Environmental Fate Date Summary
Agency has reviewed the following ecotoxicity studies for silver zeolites

Table 4
ECOLOGICAL TOXICITY PROFILE FOR SIVLER (COPPER AND ZINC) ZEOLITE

Guideline#/Study type	MRID#/Reference	Dosing/animal Information	Results
850.1010/aquatic invertebrate acute toxicity test/frsh water Daphnid	MRID# 42032703 Ward et.al(1991)Acute Flow through toxicity of silver zeolite to Daphnid, Daphnia Magna, CORE MINIMUM	Silver zeoilte was tested at nominal conc. Of 0.06,0.10,016,0.24, and 0.40 mg/L, Purity : 99% a.i.	48 hour LC_{50} =0.28 mg/L LC_{50} = 0.035 mg/L NOEC = 0.13 mg/L
850.1075/Aquatic acute toxicity test (Bluegill sunfish)	MRID# 41651813 Ward et.al (1990) Acute flow-through toxicity of silver zeolite to Bluegill, Lepomis macrochirus		
850.1075/Aquatic acute toxicity(Rainbow Trout	MRID# 41515814 Ward et.al: acute flow-through toxicity to silver zeolites to Rainbow trout, Oncorhynchus mykiss SUPPLEMENTAL	Silver zeolite was tested at nominal conc. Of the total product, which is 4% silver and 6% copper Note: silver copper zeolite is moderately toxic to bluegill sunfish with an LC_{50} = 3.4 ppm	96 Hour LC_{50} =100 ppm
850.2100: Avian acute oral toxicity test (bobwhite quail)	MRID# 42871001 Campbell et al/Acute oral toxicity study with the Northern Bobwhite CORE	Silver zeolite was tested at conc. Of 292, 486, 810, 1350 and 2250 mg/kg levels: 5 quail/sex/dose Purity: > 99 % a.i.	96 Hour LD_{50} > 2250 mg/kg/non-toxic (3.4% silver and 6.1% copper)
850.2200: Avian acute dietary toxicity (bobwhite quail)	MRID# 42870901 Campbell et al (1993)a dietary LC_{50} study with Northern Bobwhite	Silver zeoilite was tested at conc. Of 562, 1000, 1780, 3160, and 5620 ppm Bobwhite quail; Purity: > 99% a.i.	LC_{50} for silver zeolite is > 5620 ppm/non-toxic (3.6% silver and 6.1 % copper)

	CORE		
850.2200 Avian Acute dietary toxicity (Bobwhite quail)	MRID#: 41615812 Culotta et.al (1990); a dietary LC_{50} study with Bobwhite		
850.2200: Avian acute dietary toxicity (Mallard Duck)	MRID#: 41615811 Culotta et.a l (1990); a dietary LC_{50} study with Mallard		

Table 5

ENVIRONMENTAL FATE PROFILE OF SILVER ZEOLITE(COPPER AND ZINC)

Guideline #/ Study Type	Reference Information	Results
835. 1230: Leaching/adsorption/desorption of silver zeolite (copper and zinc)	MRID#; 416151818; Harris et al. (1990); silver and copper zeolites: leaching of copper and silver from impregnated polymers	Under Review
835.1230: Leaching adsorption/ desorption of silver zeolites (copper and zinc)	MRID 42245401; Loveday et al. (1992): Environmental fate data leaching study with Bactekiller AC	Under Review
835.2120: hydrolysis of silver zeolite (copper and silver)	MRID#: 41615816; Harris et al (1990).: silver copper zeolite; release of silver and copper under hydrolysis conditions	Under Review
835.2120: hydrolysis of silver zeeolite (copper and silver)	MRID# 43032806; Kyranos et al. (1991); silver zinc zeolite: release of silver and zinc under hydrolysis conditions	Under Review
835.2240: photolysis of silver copper zeolite in water	MRID#: 41615817; Harris et al.; (1990); release of silver and copper under per photolysis conditions in water	Under Review
835.2120: hydrolysis of silver copper zeolite	MRID#: 41615186; Harris et al (1990); release of silver and copper under hydrolysis conditions	Under Review
835.2120: hydrolysis of silver and zinc from silver zinc zeolite	MRID#: 43032806; Kyranos et al (1991); release of silver and zinc from silver zinc zeolite under hydrolysis	Under Review

	conditions	
835.2240: Photodegradation in water of silver copper zeolite	MRID#: 00158969; Harris et al (1990); release of silver and copper under aquatic photolysis conditions	Under Review

Environmental fate Data Gaps: Only following two studies are needed.

GLN 850.6800) modified activated sludge respiration inhibition;

(GLN 835.1110) activated sludge sorption isotherm

The Agency is in the process of completing the reviews on these studies
Environmental Fate Data: Environmental fate risk assessment will be completed with the completion of fate data reviews.
The Agency has also noted that these pesticides are also used in shingles. A special leaching study will be required for risk assessment. There are no guideline studies for such leaching studies. The registrant should develop the protocols to conduct such a study and get approval from the Agency before conducting the study for the completion of data requirements

SILVER SODIUM, HYDROGEN ZIRCONIUM PHOSPHATE

REGISTRATION REVIEW DECISION

PRODUCT CHEMISTRY, ENVIRONMENTAL FATE AND ECOLOGICAL EFFECTS SUMMARY
PC Code: 072560; Case No. 4082

Introduction:

Silver sodium hydrogen zirconium phosphate was first registered for use as a pesticide in the United States in 2000 for use as a material preservative to be incorporation during the manufacturing process. There are currently five (5) active products and one pending product. There are no inert uses for this chemical.

The current active product is a material preservative for incorporation into apparel, plastic, paper coatings, paints, adhesives, film and molded plastics. Food contact uses include ice making equipment (water pans, piping, tubing, guards, ice storage bins, trays, ice scoops, buckets, valves, and gaskets); drinking water contact materials (water bottles, cups, gaskets, plumbing fixtures, storage tanks and vessels, water piping, tubing, valves, spigots, coolers, water dispensing components, housing units, and water filter components).

Table 1 Case 4082 Silver Compounds Appendix A PC code 072560-Silver Sodium Hydrogen Zirconium Phosphate

Table 1. Registered Active Products of Silver sodium hydrogen zirconium phosphate

EPA Reg. Number	Product Name	Formulation Type	Percent Active Ingredient	Registrant
11631-2	Antimicrobial AlphaSan® RC 5000	Technical Chemical (powder)	99.9	Milliken Chemical
11631-3	Antimicrobial AlphaSan® RC 2000	Technical Chemical (powder)	99.9	Milliken Chemical
11631-4	Antimicrobial AlphaSan® RC 7000	Formulation Intermediate (powder)	31	Milliken Chemical
74079-1	Antimicrobial Novaron® AG300	Crystalline	99.9	Toagosei America, Inc.
74079-2	Antimicrobial Novaron® AGZ330	Formulation, Manufacturing Chemical (powder)	31	Toagosei America, Inc.

Table 2

Chemical Identity: Silver Hydrogen Sodium Zirconium Phosphate

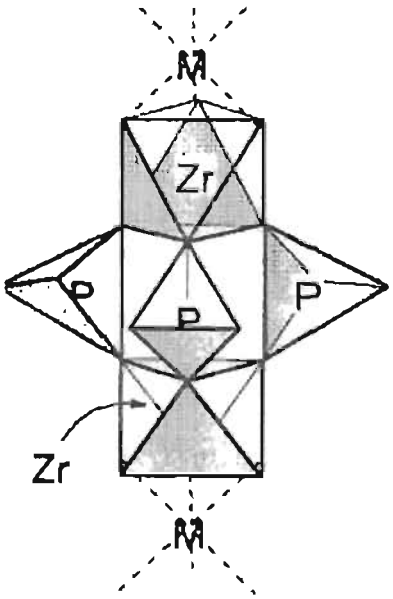
Table 2. Chemical Identity	
Common Name	Alphasan
Chemical Name	Silver Sodium Hydrogen Zirconium Phosphate
IUPAC	Not Known
Molecular Weight	481-531
PC Code	072560
CAS Registry Number	265647-11-8
Molecular Formula	$Ag_{(0.1-0.5)}Na_{(0.1-0.8)}H_{(0.1-0.8)}Zr_2(PO_4)_3$
Registration Review Case No.	4082
Registration Review Case Name	Silver and Compounds
Classification:	Inorganic
Chemical Structure::	 **Unit Cell Bonded to M**

Table 3

Physical/Chemical Properties for Silver / Sodium/ Hydrogen/Zirconium Phosphate

Guideline No.	Physical and Chemical Properties	Value
830.1550	Product identity and composition	Refer to Table 2
830.1600	Description of materials used to produce the product	CBI
830.1620	Description of production process	CBI
830.1650	Description of formulation process	CBI
830.1670	Discussion of formation of impurities	CBI
830.1700	Preliminary analysis	CBI
830.1750	Certified limits	CBI
830.1800	Enforcement analytical method	The Agency will need this data for this chemical
830.1900	Submittal of samples	NA
830.6302	Color	White
830.6303	Physical State	Solid finePowder[1]
830.6304	Odor	Odorless
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable
830.6314	Oxidation/Reduction: Chemical Incompatibility	Redox reactions do not occur
830.6315	Flammability Flash Point	Not flammable
830.6316	Explodability	Not explosive
830.6317	Storage Stability	Stable indefinitely
830.6319	Miscibility	NA
830.6320	Corrosion Characteristic	None
830.6321	Dielectric breakdown voltage	NA
830.7000	pH	NA
830.7050	UV/Visible absorption	NA
830.7100	Viscosity	NA
830.7200	Melting Point	> 1300 ° C
830.7220	Boiling point	NA
830.7300	Density	3.0 g/cm3[1]
830.7370	Dissociation Constants in water	1×10^{-13}
830.7520	Particle size[2]	See note 2
830.7550	Octanol/water partition coefficient (K_{ow})	NA
830.7840	Solubility in water	< 10 µg/L in water
830-xxxx	Solubility in organic solvents in g/100 ml	Less soluble in organic solvents
830.7950	Vapor pressure	NA[1]

[1]TGAI=Technical Grade Active Ingredient; CBI= Confidential Business Information.

2: The Agency is requesting the registrants to provide the following information to the Agency regarding their silver product:

a. Does your product contain particles that are less than 500 nm in size
b. If so, provide the particle size and distribution
c. What analytical method was used to determine the size and size distribution

Science Findings:

The Agency has conducted a review of the available product chemistry, environmental fate, and ecotoxicity data for silver sodium hydrogen zirconium phosphate. The findings are summarized below.

Product Chemistry Summary

The data submitted pertaining to the physical and chemical characteristics of the active ingredient, silver sodium hydrogen phosphate are sufficient

Ecotoxicity

A number of and eco-effects data were submitted. And these eco-effects data are adequate for risk assessment for this chemical.

ECOTOXICITY PROFILE FO SILVER ZIRCONIUM PHOSPHATE

Guideline#/Study Type	MRID#/Reference	Dosing and animal information	Results
850.1010: aquatic invertebrate acute toxicity test, fresh daphnids	MRID#: 45252302 Palmer et al. (2000); a 48 hour static study with Claderan (Daphnia Magna) AlphaSan CORE	Zirconium 33.1%, 9.8 % silver Daphnia Magna: < 24 hour old; 20 Daphnids/dose Dose levels were: 10, 100, and 1000 µg/L Defintive test: control and 5 nominal treatment levels were: 20, 40, 80, 160, 320 µg/L	Results: 48 hour EC_{50} (95% C.I.) = 23 (18-42) µg/L NOEC = 15 µg/L Validated Results: 48 hour EC_{50} (95% C>I>) = 27 (25-30 µg/L NOEC = 15 µg/L VERY HIGHLY TOXIC
850.1075: fish acute toxicity test, fresh water and marine	MRID#: 45252301; Palmer et. Al; AlphaSan RC 5000: a 96 hour static acute toxicity test with rainbow trout (Oncorhynchus	Rainbow trout (Oncorhynchus mykiss): 20 fish/dose Control and nominal treatment levels were: 78, 160, 310, 630, 1300,	Results: 96 hour LC_{50}(95% C.I.) = 643 (502-948)µg/L NOEC = 236 µg/L Verified Results:

	mykiss) CORE	and 2500 mg/L Purity: 33.1% zirconium, and 9.8% silver	96 hour LC_{50} (95% C.I.) = 689 (642-735)µg/L NOEC = 236 µg/L

TERRESTRIAL WILDLIFE

850.2100; Acute oral toxicity test	MRID#: 44582921; Helsten et. Al (1998); Avian oral toxicity test: AlphaSan RC 5000 SUPPLEMENTAL	Bobwhite quail (Colinus virginainus); 5 /sex/dose; observed for at least 14 days In 10 day range finding test: does levels were: 500, 1000 and 2000 mg/kg Definitive test: one nominal conc .of 2000 mg/kg Purity: 100% of a.i.	LD_{50} > 2000 mg/kg NOEC = 2000 mg/kg

Environmental fate data for these chemicals were not submitted. The Agency considers the current environmental fate guideline studies inadequate and intends to take a new approach for metals as outlined later in the document. Only following two studies are needed.

Environmental Fate Data Gaps:

GLN 850.6800) modified activated sludge respiration inhibition;

(GLN 835.1110) activated sludge sorption isotherm

Following is a general process for Eco-Effects Risk Assessment Risk Characterization For Silver and Compounds for the registration review:

The last comprehensive (for that time frame) document was put out by the Agency was he Silver RED which was published in 1992. Since publication of the Silver RED three synoptic reviews of silver ecotoxicity data and risks to the environment have been published as follows:

1.) Eisler, R. 1996. "Silver Hazards To Fish, Wildlife, and Invertebrates: A Synoptic Review". Bio. Rpt. 32, Contaminant Hazard Reviews, September 1996. Patuxent Wildlife Research Center, U.S. National Biological Service, U.S. Dept. of Interior, Laurel, MD 20708. pp.63.

2.) Howe, P.D. and S. Dobson. 2002. "Silver and Silver Compounds: Environmental Aspects". Concise International Chemical Assessment Document 44. Centre for Ecology and Hydrology, Monks Wood, United Kingdom. World Health Organization.

pp.34.

3.) USEPA, WQC. 2007. "2007 Draft Update Of Ambient Water Quality Criteria For Silver". October 19, 2007. Contributors: Gorsuch, J. M. Rooni, W.K. Bing, P. Paquin, R. Santore, K. Brix. Pg. 27-37.

All three have provided us with important and new information and data, which makes it imperative to re-assess the methods of risks and risk assessment. The salient data provided by these documents and decisions are summarized as follows:

Available ecotoxicity data for silver indicates that silver chloride is **practically nontoxic to birds** (LD50: >2250 mg/Kg, MRID 46453301, 99.6% silver chloride) but is **very highly toxic to aquatic animals and plants** (all types of freshwater and marine including fish, invertebrates, mollusks, frogs, insects, protozoa, algae). Numerous studies provide a wide range of ecotoxicity EC, LC, and NOAEC values depending on the silver formulation used in the study and other experimental variables. Silver ion is considered by researchers to be the most biologically available form of silver. Silver nitrate is considered to be more toxic to aquatic organisms than silver thiosulfate, silver chloride, or silver sulfide (Eisler, 2007 – pg. 9). Researchers acknowledge that little is known of the biocidal properties of Ag2+ and Ag3+ that are active ingredients in disinfectants and used increasingly in water purification systems (Eisler, 2007 – pg. 50).

The most sensitive endpoints summarized from literature for silver ion are:

ACUTE AQUATIC ORGANISM ENDPOINTS

Aquatic Organism	EC/LC50 - ug/L (ppb) toxicity
Freshwater Invertebrate – (Daphnia magna)	0.19 (EPA, MRID0005496)
Marine Invertebrate – American oyster (Crassostrea virginica)	5.80 (Eisler, 1996)
Freshwater Fish – Fathead minnow (Pimephales promelas)	1.20 (WQC, 2007)
Marine Fish – Summer Flounder (Paralichthys dentatus)	4.70 (WHO, 2002)
Freshwater Plant – algae (Scenedesmus sp.)	50.00 (Estimate) (WHO, 2002)
Marine Plant – algae (Prorocentrum mariaelebouriae)	3.30 (WHO, 2002)
Terrestrial Plant – lettuce (Lactuca sativa)	>750.00 seedling emergence (WHO, 2002)
Amphipod – (Hyalella azteca)	1.90 (WHO, 2002)
Leopard Frog – (Rana pipiens)	10.00 (WHO, 2002)
Insect – Stonefly (Pteronarcys californica)	2.50 (Eisler, 1996)
Protozoa – (Spirostomum ambiguum)	8.80 (Eisler, 1996)

CHRONIC AQUATIC ORGANISM ENDPOINTS

Aquatic Organism	NOAEC - ug/L (ppb) toxicity
Freshwater Invertebrate – (Daphnia magna)	3.22 (21 day, survival) (WQC, 2007)
Marine Invertebrate – Mussel (Mytilus edulis)	1.00 (21 day LOAEL, growth) (WHO, 2002)
Freshwater Fish – Rainbow trout (Oncorhynchus mykiss)	0.17 (18 month LOAEL survival) (WHO, 2002)
Marine Fish – Winter Flounder (Pleuroneates	10.00 (60 day depressed liver activity)

americanus)	(Eisler, 1996)
Amphipod – (Hyalella azteca)	0.95 (21 day survival) (WHO, 2002)
Insect – Mayfly (Isonychia bicolor)	0.30 (14 day molting inhibition (WHO, 2002)

BIO-CONCENTRATION FACTORS (BCF's)

Source	Aquatic Organism	BCF
Eisler, 1996	Freshwater Plants	200X
Eisler, 1996	Marine Algae	13,000 – 66,000X
Eisler, 1996	Protozoa	7,000 – 40,000X
Eisler, 1996	Fish – Common Carp (Cyprinus carpio) (41 day exposure, 42 day depuration)	73X (at 41 days) 866X (at 41 days in liver) 560X (at 41 days in digestive tract) 299X (at 41 days in kidneys) 155X (at 41 days in spleen) 109X (at 41 days in bladder) (1/3 of silver remained after depuration for 42 days)
Eisler, 1996	Fish – Brown trout (Salmo trutta) (57 days exposure, 28 days depuration)	2.7X (70% in liver, no change during depuration, 282X liver BCF)
WHO, 2002 (pg. 11)	California blackworm (Lumbriculus variegates) (28 day exposure)	0.18X
WHO, 2002 (pg. 10)	Grass shrimp (Palaemonetes pugio)	70 – 4,000X
WHO, 2002 (pg. 9)	Diatom Brown algae Mussels Scallops Oysters	210X 240X 330X 2,300X 18,700X
Eisler, 1996	Caribou (Rangifer tarandus)	3.0X bone 1.3X kidney 80X liver 0.3X muscle

Environmental Levels of Silver

- Silver ranks 67th in order of natural abundance in the Earth's crust (WHO, 2002)
- Silver tends to be elevated in crude oil and water from hot springs and steam wells (WHO, 2002).
- Silver concentrations in biota were greater in organisms near sewage outfalls, electroplating plants, mine wastes, and silver iodide-seeded areas (WHO, 2002).
- Approximately 30-70% of silver in surface waters in the US is attached to suspended particles depending on water hardness and salinity (WHO, 2002).
- Background silver level in rivers, lakes, and estuaries from pristine, unpolluted areas is approximately 0.01 ug/liter (WHO, 2002).
- Background silver levels in urban and industrial areas range from 0.01 to 0.1 ug/liter (WHO, 2002).
- Silver can remain attached to ocean sediments for approximately 100 years under conditions of high pH, high salinity, and high sediment concentrations of iron, manganese

oxide and organics (WHO, 2002).

- Maximum concentrations of total silver recorded in field collections of living organisms were 1.5 mg/Kg silver dry weight in liver of marine mammals; 2.0 in liver and 6.0 in bone of trout; 7.0 in kidneys and 44.0 in liver of birds; 14.0 in marine algae and macrophytes; 30.0 in annelid worms; 110.0 in whole mushrooms; 133.0 to 185.0 in soft parts of clams and mussels; and 320.0 in whole gastropods BCF's are variable among species of mussels (WHO, 2002).
- Benthic bivalve mulluscs can take up silver from sediment. The accumulation of silver by benthic organisms from marine sediment is attributed, in part, to the formation of stable complexes of silver with chlorine, which, in turn, favors the distribution and accumulation of silver. The ½ life persistence of silver is 149 days in the American oyster and 26 days in the Pacific oyster (WHO, 2002).
- Marine annelids and clams accumulate dissolved and sediment-bound forms of silver. Uptake of silver from sediments by marine polycheate annelids decreased in sediments high in humic substances or copper but increased in sediments with elevated concentrations of manganese or iron (WHO, 2002).
- Terrestrial plant concentrations of silver are usually less than 0.1 mg/Kg dry weight (WHO, 2002).
- Certain algae readily accumulate silver and once incorporated is tightly bound to the cell membrane. Silver accumulation in marine algae up to 14.1 mg/Kg dry weight was due mainly to adsorption rather than uptake. Silver biocentration factors of 13,000 to 66,000X are common for algae. Algae dosed for 4 days with 0.5 and 0.05 ug/L silver and fed to marine and freshwater copepods had significant adverse effects on copepod reproduction (WHO, 2002).
- Silver concentrations in caddisflies and chironomid larvae usually reflect silver concentrations in sediments. Another study showed a high correlation of silver bioaccumulation in arthropods with lake water silver concentrations 20 days earlier (WHO, 2002).
- Relatively high concentrations of silver were found in the livers and body hair of seals and sea lions with 70% of body burden in the liver. Silver concentrations in mg/Kg body weight were 0.04 to 0.55 in Northern fur seal, 0.1 to 1.04 for Steller sea lions, and 0.03 to 0.83 for Harbour seals. Silver in Alaskan beluga whale liver was 2 orders of magnitude higher than for any other marine mammals (no adverse effects were reported (WHO, 2002).

Aquatic organisms that rely on arthropods and/or aquatic plants for the bulk of their diet may have greater potential for exposure to silver. Benthic annelids and mollusks are also expected to be exposed to higher silver concentrations from sediments.

Risk assessment and characterization integrates exposure and toxicity information to evaluate the potential for adverse ecological effects. Risk quotients (RQs) are determined for each taxa or ecological group by comparing exposure estimates (Estimated Environmental Concentrations, EECs) to the available acute and chronic ecotoxicity values, where:

RQ = Exposure estimate (EEC) / Toxicity value

RQs are compared to OPP's levels of concern (LOCs). Exceedance of an LOC indicates a potential for acute or chronic adverse effects on nontarget organisms and identifies a need for regulatory action to mitigate risk. LOCs currently address the following risk presumptions:

acute:	regulatory action may be warranted to reduce or preclude acute exposure
acute, listed species:	additional regulatory action may be warranted to protect listed (i.e., endangered or threatened) species
chronic:	regulatory action may be needed to reduce or preclude chronic exposure

The LOCs for the various risk presumptions are listed below for terrestrial and aquatic animals and plants:

	Aquatic Animals	Terrestrial Animals	Plants
Acute:	0.5	0.5	1
Acute, listed species:	0.05	0.1	1
Chronic:	1	1	n/a

The following toxicity endpoints are used as inputs to the RQ method for expressing risk:

Aquatic Animals	
Acute:	Lowest tested EC50 or LC50 for freshwater fish and invertebrates and estuarine/marine fish and invertebrates
Chronic:	Lowest NOEC for freshwater fish and invertebrates and estuarine/marine fish and invertebrates (early life-stage or full life-cycle tests)
Terrestrial Animals	
Avian acute:	Lowest LD50 (single oral dose) and LC50 (subacute dietary)
Avian chronic:	Lowest NOEC (21-week avian reproduction test)
Mammalian acute:	Lowest LD50 from single oral dose test.
Mammalian chronic:	Lowest NOEC for two-generation reproduction test
Plants	
Terrestrial:	Lowest EC25 values from both seedling emergence and vegetative vigor for both monocots and dicots
Terrestrial listed:	Lowest EC05 or NOEC for both seedling emergence and vegetative vigor for both monocots and dicots

Aquatic vascular and algae:	Lowest EC50
Aquatic vascular listed:	NOEC or EC05

When available, toxicity measures or other appropriate information from non-guideline studies or from the open literature also may be used to characterize and refine risks.

EPA generally uses computer simulation models to estimate exposure of aquatic organisms to an active ingredient (e.g, PDM-4). These models estimate EECs in surface waters and sediment using product-label information (e.g., treatment site, application rate, application method) and available environmental-fate data to determine how rapidly the pesticide degrades and its expected movement in environmental compartments.

For aquatic organisms, the following EECs are typically used to calculate the RQ for each taxa:

Fish	
Acute:	Instantaneous
Chronic:	60-day average
Invertebrates	
Acute:	Instantaneous
Chronic:	21-day average
Plants	
Acute:	Instantaneous
Chronic:	Not applicable

Endangered Species Considerations

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 C.F.R. ' 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section IIB, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment. The proposed material preservative uses fall into this category.

If it is determined that there is potential for the proposed material preservative uses to overlap with listed species and that a more refined assessment is warranted, to include direct, indirect and habitat effects, the refined assessment should involve clear delineation of the action area associated with these uses and best available information on the temporal and spatial co-location of listed species with respect to the action area. This analysis has not been conducted for this assessment. An endangered species effect determination will not be made at this time.

Environmental Fate Risk Assessment and Risk Characterization

Generally the Agency uses the following environmental fate guidelines studies for fate risk assessment and risk characterization.

Environmental Fate Studies:[1]

- 835.2120: Hydrolysis study;
- 835.2240: Photodegradation in water;
- 835.1230: Adsorption/desorption studies;
- 835.1240: Soil column leaching;
- 835.1730: Accumulation studies in fish;
- 835.4100: Aerobic soil metabolism;
- 835.4200: Anaerobic soil metabolism;
- 835.4300: Aerobic aquatic metabolism;
- 835.4400: Anaerobic aquatic metabolism;
- NGN: Aquatic leaching from wood study. (For guidance refer to: Standard Method of Determining The Leachability of Wood Preservatives, American Wood-Preservers' Association Standard E11-06);
- 835.1950: Accumulation studies in aquatic nontarget organisms; and
- 840.1100: Aquatic field study.

However the Agency now believes a new approach is needed to accomplish this task. The following statement is presented for this review and public comments. Only following two studies are needed.

Environmental fate Data gaps:

*GLN 850.6800) modified activated sludge respiration inhibition;

*(GLN 835.1110) activated sludge sorption isotherm

ENVIRONMENTAL FATE AND TRANSPORT RISK TRANSPORT FOR METALS AS BIOCIDES

A NEW APPROACH

In 2007, EPA's Risk Assessment Forum published the document **Framework for Metals Risk Assessment** (http://epa.gov/osa/metalsframework/index.htm). The Office of Pesticides Programs (OPP) wants to explore the possibility of retooling the existing fate and transport guidelines for metals risk assessment and risk characterization or design new guidelines studies for metals as biocides. While a final and complete policy formulation for the new approach will require a thorough thinking and input from all stakeholders, some background information is provided here and these along with other information will form the basis of the guiding principles for new guidelines or guidance documents for environmental fate and transport studies for metals as biocides.

Metals are ubiquitously present in the environment, most of the time as mixture of metals. Some metals are essential for physiological function in humans while others are necessary for microorganisms, plants and animals. Metals do not degrade or biodegrade like organic chemicals by any chemical or biological processes but are transformed into various other species (change of oxidation potential, formation of intermediate species, or complex formation with other inorganic or organic molecules.

Metals have a natural tendency to be absorbed, transformed, distributed and excreted from organisms. All these processes depend on the speciation of the metal, and also on the organism's ability to facilitate these processes.

Some important governing factors for metals' environmental fate and transport assessment will depend on the environmental chemistry of the metal, including metals speciation (change of physical or chemical form, oxidation state etc.). These processes in turn are dependent on pH, redox potential, cation exchange capability, moisture content, and organic matter present around metals. Consequently, environmental fate and transport and effects risks may not be the same for all forms of a metal. Moreover, the chemistry of metals in aqueous media depends on many factors, some which are: colloidal formation, pH changes, salinity, redox potential, speciation/ complexation, interactions with organic matter, biofixation of metals in microorganisms.

The chemistry of metals in sediments likewise depend on several factors, some of which are: the chemistry and composition of the sediments have a solid phase which are minerals, organic matter, pore water, oxygen content which declines with the depth (oxic vs anoxic environment), porosity of the sediments, pH changes with depth, alkalinity, and redox conditions of the sediments. Metals in sediments are accessible for chemical interactions if metals are in a dissolved state, but metals found in mineral matrices are not usually available for chemical interactions.

Metals in soils exist in as cations, anions or as neutral species. Some of these may be accessible for chemical reactions and some may be covalently or ionically bonded.
Cation exchange capacity depends on charge density and valence of the cation involved:
H > Al> Ca> Na etc.

A number of physical /chemical characteristics are not required under the existing guidelines, but for new approach a few concepts from the following tentative list will become important for risk assessment and risk characterization for metals as biocides:

1. Class of metal: representative, transition/inner transition, metalloid
2. Common and or most stable oxidation state (+1, or + 2 or if a metal shows multiple oxidation states)
3. Redox potentials in water: under acidic and basic conditions
4. Redox potentials in soil (4 representative soil)
5. Solubility in water
6. Kds: How strongly a metal binds with soils (4 representative soils)
7. Kocs
8. UV spectra of transition or inner transition metal used as biocides where there are more than one oxidation states, spectra for all relevant oxidation states may be provided.
9. pH /solubility profile of the metal biocide at various pHs.

Because of these and other factors not mentioned here, new environmental fate and transport guideline studies or guidance documents will need to be be developed by OPP
Depending on the exposure routes (air, water, soil, sediment, biota, plants) new assessment models and amended aquatic and terrestrial models will be developed for the risk assessment for metals as biocides. Some of these models will likely be use-site specific

APPENDICES

DATA GAPS AND JUSTIFICATIONS
Environmental Fate of Silver and Silver Salt

RR Case Name	PC Codes	CAS #
Silver	072501	7440-22-4
Silver sulfate	072511	10294-26-5
Silver nitrate	072503	7761-88-8
Silver chloride	072506	7783-90-6
Silver oxide	129097	155645-89-

Appendix A

Guideline	Study Title	Practical Utility of Data
GLN(850.6800)	Modified activated sludge respiration inhibition;	**1) What is the value of the study?** The modified activated sludge, respiration inhibition test would allow EPA to identify antimicrobial pesticides which could harm microorganisms found in biological wastewater treatment systems and would also help establish correct concentrations for use in the ready biodegradability test. **2) How would the data be used?** The data would be used to determine the potential of silver and silver salts to directly harm the nontarget organisms and/or to microbial treatment processes present in a WWTP and to determine suitable noninhibitory concentrations of zinc oxide to be used in biodegradability tests. **3) How could the data affect the risk assessment?** If the data shows that silver and silver salts is toxic to nontarget organisms and/or to microbial process found in WWTPs then, the Agency may need Tier II environmental fate data to evaluate potential adverse effects on WWTPs. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the potential exposure of silver and silver salts to waste water treatment plants (WWTPs) (via effects on WWTP microbes).
GLN (GLN 835.1110)	Activated sludge sorption isotherm	**1) What is the value of the study?** The results from activated sludge sorption study would allow EPA to assess the distribution of the antimicrobial among the solid, aqueous, and vapor phases of WWTPs. Specifically, this study identifies those chemicals which sorb to sludge biomass. **2) How would the data be used?** The data would be used to determine the sorption potential of silver and silver salts to activated sludge biomass and in biological wastewater treatment systems.

		3) How could the data affect the risk assessment? If zinc oxide is not sorbed or biodegraded then, it would pass through a biological treatment system unaffected and it may contaminate surface and drinking waters and also may have potential adverse effects to nontarget organisms. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the sorption potential of activated sludge for the removal of specific chemical compounds in biological wastewater treatment systems.

DATA GAPS AND JUSTIFICATIONS

Environmental Fate of Silver Zeolites (Copper and Zinc)

RR Case Name	PC Codes	CAS #
Silver Zeolite	221700	130328-19-7

Appendix B

Guideline	Study Title	Practical Utility of Data
GLN(850.6800)	Modified activated sludge respiration inhibition;	**1) What is the value of the study?** The modified activated sludge, respiration inhibition test would allow EPA to identify antimicrobial pesticides which could harm microorganisms found in biological wastewater treatment systems and would also help establish correct concentrations for use in the ready biodegradability test. **2) How would the data be used?** The data would be used to determine the potential of silver zeolites (copper and zinc) to directly harm the nontarget organisms and/or to microbial treatment processes present in a WWTP and to determine suitable noninhibitory concentrations of zinc oxide to be used in biodegradability tests. **3) How could the data affect the risk assessment?** If the data shows that silver and silver salts is toxic to nontarget organisms and/or to microbial process found in WWTPs then, the Agency may need Tier II environmental fate data to evaluate potential adverse effects on WWTPs. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the potential exposure of silver zeolites to waste water treatment plants (WWTPs) (via effects on WWTP microbes).
GLN (GLN 835.1110)	Activated sludge	**1) What is the value of the study?** The results from activated sludge sorption study would allow

	sorption isotherm	EPA to assess the distribution of the antimicrobial among the solid, aqueous, and vapor phases of WWTPs. Specifically, this study identifies those chemicals which sorb to sludge biomass. **2) How would the data be used?** The data would be used to determine the sorption potential of silver zeolites (copper and zinc) to activated sludge biomass and in biological wastewater treatment systems. **3) How could the data affect the risk assessment?** If zinc oxide is not sorbed or biodegraded then, it would pass through a biological treatment system unaffected and it may contaminate surface and drinking waters and also may have potential adverse effects to nontarget organisms. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the sorption potential of activated sludge for the removal of specific chemical compounds in biological wastewater treatment systems.

DATA GAPS AND JUSTIFICATIONS
Environmental Fate of Silver Sodium Hydrogen Zirconium Phosphate

RR Case Name	PC Codes	CAS #
Silver/Na/H/Zr Phosphate	072560	265647-11-8

Appendix C

Guideline	Study Title	Practical Utility of Data
GLN(850.6800)	Modified activated sludge respiration inhibition;	**1) What is the value of the study?** The modified activated sludge, respiration inhibition test would allow EPA to identify antimicrobial pesticides which could harm microorganisms found in biological wastewater treatment systems and would also help establish correct concentrations for use in the ready biodegradability test. **2) How would the data be used?** The data would be used to determine the potential of silver Na/H/Zr Phosphate to directly harm the nontarget organisms and/or to microbial treatment processes present in a WWTP and to determine suitable noninhibitory concentrations of zinc oxide to be used in biodegradability tests. **3) How could the data affect the risk assessment?** If the data shows that silver and silver salts is toxic to nontarget

		organisms and/or to microbial process found in WWTPs then, the Agency may need Tier II environmental fate data to evaluate potential adverse effects on WWTPs. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the potential exposure of Silver Na/H/Zr Phosphate to waste water treatment plants (WWTPs) (via effects on WWTP microbes).
GLN (GLN 835.1110)	Activated sludge sorption isotherm	**1) What is the value of the study?** The results from activated sludge sorption study would allow EPA to assess the distribution of the antimicrobial among the solid, aqueous, and vapor phases of WWTPs. Specifically, this study identifies those chemicals which sorb to sludge biomass. **2) How would the data be used?** The data would be used to determine the sorption potential of silver Na/H/Zr Phosphate to activated sludge biomass and in biological wastewater treatment systems. **3) How could the data affect the risk assessment?** If zinc oxide is not sorbed or biodegraded then, it would pass through a biological treatment system unaffected and it may contaminate surface and drinking waters and also may have potential adverse effects to nontarget organisms. **4) What is triggering the need for this data?** Studies are needed to conduct environmental fate assessment and to determine the sorption potential of activated sludge for the removal of specific chemical compounds in biological wastewater treatment systems.

APPENDIX D

DATA GAPS AND JUSTIFICATIONS
Product Chemistry Data Gaps for Elemental Silver

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
830.1550	Product identity and composition	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety.
830.1600	Description of materials used to produce the product	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		form the basis for labeling and product safety
830.1620	Description of production process	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1650	Description of formulation process	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1670	Discussion of formation of impurities	**1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1700	Preliminary analysis	***1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1750	Certified limits	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1800	Enforcement analytical method	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1900	Submittal of samples	**1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6313	Stability to sunlight, normal and elevated temperature, metals/metal ions	Stable to sunlight and metal/metal ions[1]
830.6314	Oxidation/Reduction: Chemical Incompatibility	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6315	Flammability Flash Point	**1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6316	Explodability	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6317	Storage Stability	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,.

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		2) How would the data be used? This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6319	Miscibility	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6320	Corrosion Characteristic	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
830.6321	Dielectric breakdown voltage	*1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830-7840	Solubility in organic solvents in g/100 ml	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety

APPENDIX D
DATA GAPS AND JUSTIFICATIONS
Product Chemistry Data Gaps for Silver Sulfate

Guideline No.	Physical and Chemical Properties	Practical Utility of Data
830.1800	Enforcement analytical method	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830-xxxx	Solubility in organic solvents in g/100 ml	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety

APPENDIX E
DATA GAPS AND JUSTIFICATIONS
Product Chemistry Data Gaps for SILVER NITRATE

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
830.1600	Description of materials used to produce the product	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1620	Description of production process	*) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1700	Preliminary analysis	1) **What is the value of the study?**

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1800	Enforcement analytical method	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1900	Submittal of samples	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and

Guideline No.	Physical and Chemical Properties	Practical Utility of the Data
		the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety

APPENDIX F
DATA GAPS AND JUSTIFICATIONS
Product Chemistry Data Gaps for SILVER OXIDE

Guideline No.	Physical and Chemical Properties	Value
830.1600	Description of materials used to produce the product	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1620	Description of production process	1) **What is the value of the study?** This data are needed to support the

Guideline No.	Physical and Chemical Properties	Value
		registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1650	Description of formulation process	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1670	Discussion of formation of impurities	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements

Guideline No.	Physical and Chemical Properties	Value
		are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1700	Preliminary analysis	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1750	Certified limits	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects

Guideline No.	Physical and Chemical Properties	Value
		and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1800	Enforcement analytical method	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.1900	Submittal of samples	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with

Guideline No.	Physical and Chemical Properties	Value
		the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6314	Oxidation/Reduction: Chemical Incompatibility	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6315	Flammability Flash Point	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?**

Guideline No.	Physical and Chemical Properties	Value
		This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6316	Explodability	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6317	Storage Stability	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6319	Miscibility	1) **What is the value of the study?**

Guideline No.	Physical and Chemical Properties	Value
		This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6320	Corrosion Characteristic	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.6321	Dielectric breakdown voltage	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and

Guideline No.	Physical and Chemical Properties	Value
		the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.7000	pH	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.7100	Viscosity	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and

Guideline No.	Physical and Chemical Properties	Value
		information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety
830.7200	Melting Point	1) **What is the value of the study?** This data are needed to support the registration to allow EPA to evaluate the potential of the product to cause unreasonable adverse effects on man and the environment. The data requirements are intended to generate data and information necessary to address concerns pertaining to the identity, composition, potential adverse effects and the environmental fate of each product. Product chemistry data requirements are comprised of product identity and composition data along with the physical and chemical characteristics of a pesticide chemical,. **2) How would the data be used?** This is basic information about the chemical which ensures chemical identity and is used to form the basis for labeling and product safety

Attachment 7

Environmental Decision Memo for Food Contact Notification No. 1569

Return to inventory listing: **Inventory of Environmental Impact Decisions for Food Contact Substance Notifications (http://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN)** or the **Inventory of Effective Food Contact Substance Notifications (http://www.accessdata.fda.gov/scripts/fdcc/?set=FCN)**.

See also **Environmental Decisions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm)**.

Date: September 24, 2015

From: Biologist, Regulatory Team 2, Division of Biotechnology and GRAS Notice Review (HFS-255)

Subject: FCN No. 1569 – A solution of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip to reduce the pathogen populations on poultry carcasses, parts and organs. For use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses parts and organs, provided that the residual level of silver ion on the processed poultry is no greater than 0.071 ppm. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.

Notifier: Pure Bioscience, Inc.

To: Marla Swain, Ph.D., Division of Food Contact Notifications (HFS-275)
Through: Suzanne Hill, Environmental Supervisor, Office of Food Additive Safety, HFS-255____

Attached is the Finding of No Significant Impact (FONSI) for food-contact notification (FCN) 1569. After this notification becomes effective, copies of this FONSI and the notifier's environmental assessment, dated September 1, 2015, may be made available to the public. We will post digital transcriptions of the FONSI and the environmental assessment on the agency's public website.

Please let us know if there is any change in the identity or use of the food-contact substance.

Leah D. Proffitt

Attachment: Finding of No Significant Impact

FINDING OF NO SIGNIFICANT IMPACT

A food-contact notification (FCN No. 1569), submitted by Pure Bioscience, Inc., to provide for the safe use of a solution of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip to reduce the pathogen populations on poultry carcasses, parts and organs. For use at

levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to poultry carcasses parts and organs, provided that the residual level of silver ion on the processed poultry is no greater than 0.071 ppm. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.

The Office of Food Additive Safety has determined that allowing this notification to become effective will not significantly affect the quality of the human environment and, therefore, will not require the preparation of an environmental impact statement. This finding is based on information submitted by the notifier in an environmental assessment, dated September 1, 2015, as summarized below.

The FCS is intended to inhibit the growth of undesirable or pathogenic microorganisms, and will be used as a spray in poultry processing facilities throughout the United States. The FCS will be applied at a rate of 0.75 - 1 gal/min (gpm) via 4 to 6 spray nozzles. Disposal will be via onsite wastewater treatment ultimately to a publicly-owned treatment works (POTW). Based on industry knowledge of typical water use in the poultry industry, a volume of 0.75 to 1 gal per minute of diluted antimicrobial is expected be used for a 4 to 6 nozzle spray cabinet that serves to coat the surfaces of the carcasses, parts or organs. Maximum component concentration in the FCS concentrate is:

- Silver 0.24%
- Sodium Lauryl Sulfate (SLS) 2.4%
- Citric acid 20%

Applying the above-noted 1 gpm use statistic yields an 8-hour use rate of 480 gallons, or 960 gallons for plants operating a 16-hour day. The FCS dilution rate will be 1:80 (for the maximum use rate of 30 ppm). Thus, a 16-hr plant using 960 gallons of diluted FCS per day equates to 960/80 = 12 gallons of silver dihydrogen citrate (SDC) concentrate per day.

A processing rate of 250,000 carcasses per day is assumed, using 5 – 8 gal of water per carcass per day as reported in the 2004 study by Northcutt and Jones. Using the processing rate of 250,000 carcasses per day, at 5 – 8 gal water per carcass per day, yields 1.25 million gal waste water per day. It is further assumed that all of the FCS will be discharged to the onsite wastewater treatment facility, and that daily effluent volume is 1.25 million gallons, or 4.74 million liters. The FCS components in this daily effluent are as follows:

- Silver: 120 g/ 4.74 million liters = 253 ng/liter (ppt).
- SLS: 1190 g/4.74 million liters = 2.5 µg/liter (ppb).
- Citric acid: 10,000 g/4.74 million liters = 2.1 mg/liter (ppm).

Treatment of the process water at the on-site wastewater treatment plant is expected to result in near complete biodegradation (90%) of the organic components of the SDC solution (citric acid, citrate and SLS). Furthermore, silver is expected to partition at 94% to sludge and 6% to waste water. Thus, the environmental introduction concentrations (EICs) are as follows:

- Silver(water): 253 ng/L x 6% partitioning to water = 15 ng/L (ppt)
- 15 ng/L (ppt) ÷ 10 (dilution in POTW or surface water) = 1.5 ng/L
- Silver(sludge): 253 ng/L (ppt) x 94% partitioning to sludge = 238 ng/L
- SLS: 2.5 µg/L (ppb) ÷ 10 ÷ 10 = 0.025 µg/L = 25 ng/L*
- Citric acid: 2.1 mg/L (ppm) ÷ 10 ÷ 10 = 0.021 mg/L = 21 µg/L*

* We divide by 10 twice to account for 90% degradation and 10-fold dilution

Pursuant to 40 CFR 261.24, silver is a toxic hazardous waste—carrying a waste code of D011—if detected at 5 mg/L by Toxicity Characteristic Leaching Procedure (TCLP) - EPA Method 1311. Accordingly, if not sent for silver recovery, sludge containing more than 5 mg/L silver TCLP must be managed and disposed of as a hazardous waste. However, silver in sludge is estimated at 238 ng/L, as shown above. This concentration is 20,000-fold lower than the level requiring disposal of the sludge as toxic waste. Therefore, EPA's limits should be no issue with respect to disposal of sludge even from an onsite treatment facility. Only silver sulfide, and very minor amounts of silver ion, citric acid and SLS are expected to survive treatment at the on-site water treatment facilities at poultry processing plants. Silver is naturally present at low levels in the environment in surface waters at concentrations between 0.2-0.3 µg/L. The EEC in water of 1.5 ng/L is only a small fraction of the background silver levels in natural waters and will not impact the natural variation of background silver. Furthermore, EPA's re-registration review of silver reports LC50 values for freshwater fish between 3.9 and 280 µg/L[1] . These values are over 2000 times larger than the EEC for silver in water (1.5 ng/L)

Therefore, the proposed use of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip to reduce the pathogen populations on poultry carcasses, parts and organs, does not present significant environmental impacts.

Prepared by _____Date: 09-24-2015 (electronically signed)
Leah D. Proffitt
Biologist
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration

Approved by _____Date: 09-25-2015 (electronically signed)
Suzanne Hill
Environmental Supervisor
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration

[1] EPA Reregistration Eligibility Decision (RED) on Silver (1992) pg. 16. Available Online at:
http://www.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-75_5-Sep-07.pdf (http://www.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-75_5-Sep-07.pdf)

More in Environmental Decisions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm)

Decisions for Food-Contact Notifications (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105897.htm)

Decisions for Petitions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105895.htm)

Definitions of Environmental Terms (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105934.htm)

1. Date: August 20, 2015

2. Name of Applicant/Petitioner: Pure Bioscience, Inc.

3. Address: Mitchell Cheeseman, Ph.D.
Steptoe & Johnson LLP
1330 Connecticut Ave. NW
Washington, DC 20036

4. Description of Proposed Action:

a. Requested Action

The action requested in this notification is the establishment of a clearance to permit the use of a solution of silver dihydrogen citrate (SDC) stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied to reduce the pathogen populations on poultry carcasses, parts and organs.

b. Need for Action

SDC solutions reduce populations of pathogenic and nonpathogenic microorganisms that may be present on poultry carcasses parts and organs and retard the spoilage of the poultry by reducing the number of spoilage-causing organisms. SDC is expected to be an important preventive control in providing safer poultry products for consumers.

The present application is in response to the changing needs of the food processing industry. Many antimicrobials previously approved for use in poultry processing have physical and chemical properties which make them more challenging to use and, therefore, less desirable for our intended use. In addition, the increasing pressure by Federal authorities to continue to improve control of foodborne pathogens in poultry processing makes it necessary to use antimicrobials such as SDC in order to achieve needed reductions in microbial populations without undesirable side effects related to worker exposure and the quality of processed poultry.[1]

c. Locations of use/disposal

This product is for use in poultry processing plants throughout the United States. The expected route of disposal for waste solution is the processing plant wastewater treatment facilities. It is expected that on-site waste water treatment facilities will discharge to publically owned treatment works (POTW) or directly to surface waters.

[1] See USDA FSIS Federal Register Notice, "New Performance Standards for Salmonella and Campylobacter in Young Chicken and Turkey Slaughter Establishments: Response to Comments and Announcement of Implementation Schedule," 76 Fed. Reg. 15282; see also FSIS Notice 54-12, "New Performance Standards for Salmonella and Campylobacter in Chilled Carcasses at Young Chicken and Turkey Slaughter Establishments," dated 9/11/12, available at http://www.fsis.usda.gov/OPPDE/rdad/FSISNotices/54-12.pdf.

The antimicrobial will be applied to the surfaces of poultry carcasses, parts, organs or trim in a spray cabinet or line. Based on our understanding of typical water use in the poultry industry and our anticipated market, we expect a volume of 0.75 to 1 gal per minute of our diluted antimicrobial will be used for a 4 to 6 nozzle spray cabinet that serves to coat the surfaces of the carcasses, parts or organs.

After the diluted product is sprayed onto the poultry, the bulk of the solution drains off of the product. The waste solution ultimately runs into drains and enters the poultry processing plant water treatment facility. All of this water is collected and treated by the facility prior to it being sent to a POTW. Very minor quantities are lost to evaporation into the air.

5. Identification of Substances that are the subject of the Proposed Action:

The raw materials used in this product are silver, citric acid, sodium lauryl sulfate, and water. The result of the reaction of silver and citric acid in the presence of SLS is to form an equilibrium stabilized complex of SDC. When the mixture is diluted for use on poultry carcasses, poultry parts and organs (1:80 or 1:160), the solution contains no more than 30 ppm silver as SDC.

Complete Name	CAS No.	Molecular Weight	Molecular Formula
Silver	7722-84-1	34.01	Ag
Citric acid	64-19-7	60.05	$C_6H_8O_7$
Sodium Lauryl Sulfate	79-21-0	76.05	$NaC_{12}H_{25}SO_4$
Water	7732-18-5	18.01	H_2O

6. Introduction of Substances into the Environment:

a. Introduction of substances into the environment as a result of manufacture:

The FCS is manufactured in plants which meet all applicable Federal, State and local environmental regulations. Pure Bioscience also asserts that there are no extraordinary circumstances pertaining to the manufacture of the FCS such as 1) unique emission circumstances are not adequately addressed by general or specific emission requirements (including occupational) promulgated by Federal, State or local environmental agencies and the emissions may harm the environment; 2) a proposed action threatens a violation of Federal, State or local environmental laws or requirements (40 CFR 1508.27(b)(10)); and 3) production associated with a proposed action may adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora to be endangered or threatened, or wild fauna or flora that are entitled to special protection under some other Federal law.

b. Introduction of substances into the environment as a result of use/disposal:

Introduction of dilute solutions of the product into the environment will take place primarily via release in wastewater treatment systems. Introduction of the components of the product into the environment will result from use of the product as an antimicrobial agent for spray or dip application onto poultry carcasses, parts and organs, and the subsequent disposal of such water and spray drainage into the processing plant wastewater treatment facility. The total amount of product used at a typical facility can be estimated, although the actual amounts used will vary, depending on equipment used and the amount of poultry processed. The example use scenario is based on the experience of the notifier and information in FDA's files.

Our expectation, based on our understanding of poultry processing and our market predictions, is that a typical poultry plant will use an antimicrobial spray, at a maximum rate of 1 gal/min, or 480 gallons per 8 hr. shift, and 960 gallons for a plant processing for 16 hr/day. For the larger 16 hr plants, a total of 960/80 = 12 gallons of SDC concentrate would be consumed per day.[2]

A typical poultry plant processing 250,000 carcasses per day will use about 5 to 8 gal of water per carcass per day. Thus, we will assume our model plant generates at least 1.25 million gallons of waste water per day.[3] The maximum concentration of each component in the concentrated product is:

- Silver 0.24%
- Sodium Lauryl Sulfate 2.4%
- Citric acid 20%

The concentrated product is 9.11 pounds per gallon, so 12 gallons would be 109.2 pounds or 49.6 kg.[4]

The total amount of each component present in 12 gallons is

- Silver: 0.24% of 49.6 kg or 0.12 kg.
- SLS 2.4% of 49.6 kg or 1.19 kg.
- Citric acid 20% of 49.6 kg or 10 kg.

Assuming that 100% of these chemicals are discharged to waste water treatment facility each day in a total waste water discharge of 1.25 million gallons from the poultry plant, the maximum concentration of these components in waste water would be:

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[2] We have applied the minimum dilution rate of 1:80 even though in some cases a dilution rate of 1:160 may be used. The higher dilution rate would reduce the amount of the FCS introduced into the environment.

[3] J.K. Northcutt and D.R. Jones: "A Survey of Water Use and Common Industry Practices in Commercial Broiler Processing Facilities," 2004; Journal of Applied Poultry Research 13:48-54.

[4] See MSDS Sheet Provided.

(Assuming total waste water of 1.25 million gallons = 4.74 million liters)

- Silver: 120 g/ 4.74 million liters = 253 ng/liter (ppt).
- SLS: 1190 g/4.74 million liters = 2.5 µg/liter (ppb).
- Citric acid: 10,000 g/4.74 million liters = 2.1 mg/liter (ppm).

Treatment of the process water at the on-site wastewater treatment plant is expected to result in near complete biodegradation of the organic components of the SDC solution (citric acid, citrate and sodium lauryl sulfate). This expectation is based on the available data on the biodegradability of SLS[5] and citric acid[6] which suggest that approximately 90% or more will biodegrade before entry into surface waters. If we assume that level of biodegradation and use FDA's standard dilution factor of 1/10 for discharge of POTWs surface waters worst case discharges of 0.021 mg/L for citric acid and 25 ng/L for SLS can be estimated.[7]

If we apply the estimate by Ratte et al. that > 94% of the silver will partition to sludge during treatment at the on-site facility[8] to the concentration exiting the processing facility (253ng/L), then the EIC for silver in water released from the on-site treatment facility would be 15 ng/L and the concentration in sludge generated at the onsite treatment facility would be 238 ng/L, the terrestrial EEC.[9] With respect to silver partitioning to sludge, EPA's Reregistration Eligibility Decision (RED) document for silver concludes that silver partitioning to sludge during wastewater treatment will be in the form of silver sulfides.[10] The silver in the water released from the on-site treatment facility will be further diluted either because it is released to surface waters or processed in a POTW. In either case, the concentration of silver in the aquatic compartment will be further diluted 10-fold to produce an EEC of 1.5 ng/L.[11] This concentration of silver is less than 1% of the background concentration in surface waters.[12] The EEC's for silver, SLS and citric acid are calculated below:

• $Silver_{(aq)}$: 253 ng/L * 6% partitioning to water = 15 ng/L (ppt)
15 ng/L (ppt) ÷ 10 (dilution in POTW or surface water) = 1.5 ng/L

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[5] OECD SIDS Assessment of Sodium Docecyl Sulfate, 1995, pg. 6.
[6] OECD SIDS Assessment of Citric Acid, 2000 and included references from that document. Specifically, Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox. Environm. Safety 3: 159-173, 1979. See specifically Table 3 Page 165.
[7] Rapaport, Robert A., 1988. Prediction of consumer product chemical concentrations as a function of publically owned treatment works treatment type and riverine dilution. Environmental Toxicology and Chemistry, 7(2), 107-115. Found online at:
http://onlinelibrary.wiley.com/doi/10.1002/etc.5620070204/abstract.
[8] Ratte, Hans Toni, Bioaccumulation and toxicity of Silver Compounds: A Review, Environmental Toxicology and Chemistry, Vol. 18, no.1, pp 89-108 1999.(Specifically pg. 89)
[9] 253 ng/L * 6% = 15 ng/L ; 253 ng/L * 94% = 238 ng/L
[10] EPA Reregistration Eligibility Decision (RED) on Silver (1992) pg. 16. Available Online at:
http://www.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-75_5-Sep-07.pdf
[11] Op Cite Rapaport.
[12] WHO (2003) Silver in Drinking Water: Background document for development of WHO Guidelines for Drinking-water Quality, pg 1.

- Silver$_{(terr)}$: 253 ng/L (ppt) * 94% partitioning to sludge = 238 ng/L
- SLS: 2.5 µg/L (ppb) ÷ 10 ÷ 10 = 0.025 µg/L = 25 ng/L[13]
- Citric acid: 2.1 mg/L (ppm) ÷ 10 ÷ 10 = 0.021 mg/L = 21 µg/L[14]

FDA has suggested that recovery of precious metals from sewage sludge may be important in reducing the environmental introductions of silver from the use of the additive. We do not dispute the significance of processes to recover rare metals from sewer sludge but we do not believe that the proposed use of the FCS will have any significant impact on such efforts. Based on our worst-case estimates of introductions of silver (120 g/d) complete recovery of all silver resulting from the use of the FCS would result in the annual recovery of about $22K worth of silver. Obviously complete recovery of silver is unlikely. Recent analysis of the cost-effectiveness of recovery of metals from sewage sludge have suggested that establishing new recovery processes may incur initial capital costs of millions of dollars.[15] Thus, it would take many decades to cover such capital costs from recovery of silver from the use of the FCS. Therefore, although we do not disagree that some silver resulting from the use of the FCS may be recovered from sewage sludge, we do not believe that the estimated introductions are of a magnitude to impact current efforts to recover precious metals from sewage sludge. However, sludge from an onsite facility may be processed at an offsite recovery facility. This would effectively eliminate environmental introductions of silver via sludge and result in no environmental impact.

Pursuant to 40 CFR 261.24, silver is a toxic hazardous waste—carrying a waste code of D011—if detected at 5 mg/L by Toxicity Characteristic Leaching Procedure (TCLP) - EPA Method 1311. Accordingly, if not sent for silver recovery, sludge containing more than 5 mg/L silver TCLP must be managed and disposed of as a hazardous waste. However, we have estimated a concentration of silver in sludge of 238 ng/L. This concentration is 20,000-fold lower than the level requiring disposal of the sludge as toxic waste. Therefore, EPA's limits should be no issue with respect to disposal of sludge even from an onsite treatment facility.

7. Fate of Emitted Components in the Environment:

Only silver sulfide, and very minor amounts of silver ion, citric acid and SLS are expected to survive treatment at the on-site water treatment facilities at poultry processing plants. Silver is naturally present at low levels in the environment in surface waters at concentrations between 0.2-0.3 µg/L.[16] Our EEC of 1.5 ng/L is only a small fraction of the background silver levels in natural waters and will not impact the natural variation of background silver. We reference EPA's reregistration review[17] which considers LC_{50}s for freshwater fish which range from 3.9 to 280 µg/L, LC_{50}s which are

[13] We divide by 10 twice to account for 90% degradation and 10-fold dilution.
[14] Ibid.
[15] M. Saniedanesh et al. Potential for Heavy Metal Recovery from Wastewater and Sewage Sludge, Proceedings of the 6th International Conference of Process Systems Engineering June 2013.
[16] Op Cite WHO, pg 1.
[17] Op Cite EPA ppg. 16-17.

more than 2000 times larger than the EEC for silver in water. In addition, EPA references EC_{50}s for freshwater invertebrates of 0.25 to 4500 µg/L, the lower value being over 100-fold higher than our EEC for silver. Finally, EPA references EC_{50}s for marine/estuarine invertebrates of between 5.8 and 150µg/L, EC_{50}s which are, at a minimum, nearly 4000-fold larger than our aquatic EEC. Thus, toxicity values for aquatic organisms exposed to silver indicate a margin of safety of at least 100-fold. Moreover, we would expect, as does EPA, the discharge of silver from POTWs or onsite treatment facilities to surface waters will be insignificant regarding the concentration of silver ion in water. This belief is based on the physical properties and reactivity of silver with ions present in the water and soil contacting the water.[18]

We have estimated an EEC of 238 ng/L of silver for the terrestrial compartment and expect that this silver will be present as silver sulfides. The equivalent concentration of silver sulfide would be 546.7 ng/L. Ratte (1999) reports a NOEC for earthworms for silver sulfide in sludge of 62 mg Ag/Kg sludge.[19] If we assume a density of sludge of 1.5g/cm^3 this NOEC would translate to about ~41 mg/L, a value which would represent a margin of safety compared to our terrestrial EEC of ~ 113,000-fold.[20] This is a significant safety margin given that our estimate of silver concentration assumes that sludge from onsite treatment facilities at a poultry facility will not be diluted by other sludge if applied to agricultural or other lands. In addition, Ratte (1999) reports NOECs for multiple terrestrial plants of 771 mg/Kg (the highest level tested).[21] All of these referenced experiments demonstrate no toxic effect for silver sulfide in sewage sludge at exposure levels much higher than our worst-case estimates of EECs. Therefore, we conclude that the requested use of the FCS has no potential for environmental impact from increased introductions of silver.

Remaining citric acid[22] and SLS[23] concentrations would be expected to continue to biodegrade in the environment.

8. Environmental Effects of Released Substances:

In the use scenario described above, waste antimicrobial solution (from application and drainage) will be directed to an on-site wastewater treatment facility. Water from such a facility will be discharged to surface waters or to a POTW. In addition, sludge from such an on-site treatment facility is expected to be applied to agricultural or other lands in combination with sludge from other sources.

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[18] Ibid.
[19] Op Cite Ratte, pg. 97.
[20] Donahue, Roy Luther; Miller, Raymond W.; Shickluna, John C. (1977). Soils: An Introduction to Soils and Plant Growth. Prentice-Hall pg. 60. ISBN 0-13-821918-4.
[21] Op Cite Ratte pg. 98.
[22] OECD SIDS Assessment of Citric Acid, 2000. Available at: http://www.inchem.org/documents/sids/sids/77929.pdf
[23] OECD SIDS Assessment of Sodium Dodecyl Sulfate, 1995. Available at: http://www.oecd.org/chemicalsafety/risk-assessment/publishedassessments.htm

Citric acid appears to be of low acute toxicity to fish, daphnia and algae.[24] The HERA project 2005 environmental risk assessment for citric acid derived a predicted no effect concentration (PNEC) of 0.8mg/L based on toxicity data of sodium citrate on fish, daphnia and algae.[25] This very conservative PNEC is nearly 40-fold above our worst case estimate of introductions (0.021 mg/L) for citric acid.

SLS also appears to be of low toxicity to aquatic organisms.[26] The OECD SIDS report references a lowest LOEC of 0.02 mg/L in Scenedesmus quadricauda. This LOEC is 3 orders of magnitude larger than our worst case estimated level of introduction for SLS (25 ng/L) for the proposed use.

EPA has thoroughly considered the toxicity of silver processed in wastewater facilities and concluded that no significant environmental risk of aquatic toxicity exists.[27] Moreover, the same EPA evaluation argues that the insoluble nature of silver sulfides will immobilize the vast majority of silver existing POTWs reducing toxic potential. We have estimated EECs for silver in the aquatic environment (1.5 ng/L) and in the terrestrial environment (238 ng/L).

As discussed above, ecotoxicity testing results of silver and silver compounds in aquatic environments and silver sulfide in terrestrial environments establish margins of safety of at least two orders of magnitude above our EECs for the aquatic compartment and over six orders of magnitude for the terrestrial compartment. Based on all of the above we conclude that approval of this food contact notification will not have any significant impact on the environment.

9. Use of Resources and Energy

The use of the Pure Bioscience product will not require additional energy resources for treatment and disposal of waste solution, as the components are adequately dealt with through existing infrastructure. The raw materials used in the production of the mixture are commercially-manufactured materials that are produced for use in a variety of chemical reactions and production processes. Energy used specifically for the production of the mixture components is not significant.

10. Mitigation Measures

As discussed above, no significant adverse environmental impacts are expected to result from the use and disposal of the dilutions of antimicrobial product. Thus, the use of the subject mixture is not reasonably expected to result in any new environmental problem requiring mitigation measures of any kind.

[24] Op Cite to OECD SIDS Assessment of Citric Acid, 2000.
[25] HERA, 2005, Substance: Citric Acid and Salts (CAS # 77-92-9; 5949-29-1; 6132-04-3).
[26] Op Cite OECD SIDS Assessment of Sodium Lauryl Sulfate 1995, ppg. 21-23.
[27] Op Cite EPA 1992, pg. 16-17.

11. Alternatives to the Proposed Action

No potential adverse environmental effects are identified herein that would necessitate alternative actions to that proposed in this Food Contact Notification.

12. List of Preparers

Dr. Mitchell Cheeseman, Steptoe & Johnson LLP, 1330 Connecticut Ave. NW, Washington DC, 20036

Dr. Cheeseman holds a Ph.D. in Chemistry from the University of Florida. Dr. Cheeseman served for 18 months as a NEPA reviewer in FDA's food additive program. He has participated in FDA's NEPA review of nearly 800 food additive and food contact substance authorizations and he supervised NEPA review for FDA's Center for Food Safety and Applied Nutrition for five and a half years from 2006 to 2011 including oversight of FDA's initial NEPA review for the regulations implementing the Food Safety Modernization Act.

13. Certification

The undersigned official certifies that the information provided herein is true, accurate, and complete to the best of his knowledge.

Date: August 20, 2015

Mitchell Cheeseman

14. References

Donahue, Roy Luther; Miller, Raymond W.; Shickluna, John C. (1977). Soils: An Introduction to Soils and Plant Growth. Prentice-Hall pg. 60. ISBN 0-13-821918-4.

Environmental Protection Agency, Reregistration Eligibility Decision: Silver (1992).

ETI H20. Material Safety Data Sheet for Axenohl. 2005.

FSIS Notice 54-12, "New Performance Standards for Salmonella and Campylobacter in Chilled Carcasses at Young Chicken and Turkey Slaughter Establishments," dated 9/11/12, available at http://www.fsis.usda.gov/OPPDE/rdad/FSISNotices/54-12.pdf.

Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests, 1979, Ecotox. Environm. Safety 3: 159-173.

HERA, 2005, Substance: Citric Acid and Salts (CAS # 77-92-9; 5949-29-1; 6132-04-3).

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OECD SIDS Assessment of Sodium Dodecyl Sulfate, 1995.

OECD SIDS Assessment of Citric Acid, 2000.

Rapaport, Robert A., 1988. Prediction of consumer product chemical concentrations as a function of publically owned treatment works treatment type and riverine dilution. Environmental Toxicology and Chemistry, 7(2), 107-115. Found online at: http://onlinelibrary.wiley.com/doi/10.1002/etc.5620070204/abstract.

Ratte, Hans Toni, Bioaccumulation and toxicity of Silver Compounds: A Review, Environmental Toxicology and Chemistry, Vol. 18, no.1, pp 89-108 1999.

Saniedanesh, M. et al. Potential for Heavy Metal Recovery from Wastewater and Sewage Sludge, Proceedings of the 6th International Conference of Process Systems Engineering June 2013.

USDA FSIS Federal Register Notice, "New Performance Standards for Salmonella and Campylobacter in Young Chicken and Turkey Slaughter Establishments: Response to Comments and Announcement of Implementation Schedule," 76 Fed. Reg. 15282 (March 21, 2011).

WHO, 2003, Silver in Drinking Water: Background document for development of WHO Guidelines for Drinking-water Quality.

Environmental Decision Memo for Food Contact Notification No. 1600

Return to inventory listing: **Inventory of Environmental Impact Decisions for Food Contact Substance Notifications (http://www.accessdata.fda.gov/scripts/fdcc/?set=ENV-FCN)** or the **Inventory of Effective Food Contact Substance Notifications (http://www.accessdata.fda.gov/scripts/fdcc/?set=FCN)**.

See also **Environmental Decisions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm)**.

Date: November 23, 2015

From: Biologist, Regulatory Team 2, Division of Biotechnology and GRAS Notice Review (HFS-255)

Subject: FCN No. 1600 – A solution of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip on fruits and vegetables intended for processing, for use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to all fruits and vegetables intended for processing. The FCS is not intended for use on any citrus fruit nor is it for use on grapes intended for winemaking. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.

Notifier: Pure Bioscience, Inc.

To: Marla Swain, Ph.D., Division of Food Contact Notifications (HFS-275)
Through: Suzanne Hill, Environmental Supervisor, Office of Food Additive Safety, HFS-255____

Attached is the Finding of No Significant Impact (FONSI) for food-contact notification (FCN) 1600. After this notification becomes effective, copies of this FONSI and the notifier's environmental assessment, dated October 23, 2015, may be made available to the public. We will post digital transcriptions of the FONSI and the environmental assessment on the agency's public website.

Please let us know if there is any change in the identity or use of the food-contact substance.

Leah D. Proffitt

Attachment: Finding of No Significant Impact

FINDING OF NO SIGNIFICANT IMPACT

A food-contact notification (FCN No. 1600), submitted by Pure Bioscience, Inc., to provide for the safe use of a solution of silver dihydrogen citrate (SDC) stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip on fruits and vegetables intended for processing, for use at levels up to 30 ppm silver dihydrogen citrate in the spray or dip applied to all fruits and vegetables intended for processing.

The FCS is not intended for use on any citrus fruit nor is it for use on grapes intended for winemaking. The FCS is not for use in combination with any other silver containing antimicrobial and is not intended to be used in chiller baths.

The Office of Food Additive Safety has determined that allowing this notification to become effective will not significantly affect the quality of the human environment and, therefore, will not require the preparation of an environmental impact statement. This finding is based on information submitted by the notifier in an environmental assessment, dated October 23, 2015, as summarized below.

The FCS is intended to inhibit the growth of undesirable or pathogenic microorganisms, and will be used as a spray or dip in fruit and vegetable processing facilities throughout the United States. All assumptions in the EA are based on a large, representative model produce processing facility using SDC which pretreats water on site before discharge, and is in possession of a National Pollutant Discharge Elimination System (NPDES) permit. Alternatively much smaller plants might discharge water to a POTW with no on site pretreatment. However other inflow for the POTW would further dilute silver and other residues. Based on confidential market volume information, it is estimated that the FCN component concentrations in waste water entering the onsite wastewater treatment facility at the above-described large processing facility will be as follows:

- Silver 18 ppb
- Sodium Lauryl Sulfate (SLS) 180 ppb
- Citric acid 1.5 ppm

Treatment of the process water at the on-site wastewater treatment plant is expected to result in near complete biodegradation (90%) of the organic components of the SDC solution (citric acid, citrate and SLS). Furthermore, silver is expected to partition at 94% to sludge and 6% to waste water. Thus, the effective environmental concentrations (EECs) are as follows:

- $Silver_{(aqueous)}$: 110 ng/L (ppt)
- $Silver_{(terrest.)}$: 16.9 µg/L
- SLS: = 720 ng/L
- Citric acid: = 4.5 µg/L

Daily use of the FCS is expected to result in enough silver partitioning to onsite-wastewater treatment sludge to make silver recovery economically feasible. Therefore, little or no silver is expected to enter the terrestrial environment from such facilities. However, if not sent for silver recovery, the EEC (16.9 µg/L) is 300 times lower than the hazardous waste TCLP [1] threshold of 5 mg/kg, so sludge would not need to be managed and disposed of as hazardous waste. For plants discharging to a POTW, all FCS concentrations will be reduced 10-fold due to other intake at the POTW; thus, the terrestrial EEC for silver (above) would be 1.7 µg/L. Only silver sulfide and very minor amounts of silver ion, citric acid and SLS are expected to survive treatment at the on-site water treatment facility. Silver is naturally present at low levels in the environment in surface waters at concentrations between 0.2-0.3 µg/L. The EPA Reregistration Eligibility Decision on silver reports LC50 values for freshwater fish between 3.9 and 280 µg/L, which is 3.5 – 240 times higher than the aquatic EEC.

Therefore, as the proposed use of silver dihydrogen citrate stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied by spray or dip to reduce the pathogen populations on fruits and vegetables intended for processing is not expected to result in significant environmental impacts, an environmental impact statement is not required.

Prepared by _____Date: 11-23-2015 (electronically signed)
Leah D. Proffitt
Biologist
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration

Approved by _____Date: 11-23-2015 (electronically signed)
Suzanne Hill
Environmental Supervisor
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition
Food and Drug Administration

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[1] **(http://wcms.fda.gov/ucm/resources/wcm/3rdparty/fckeditor/editor/fckeditor.html?InstanceName=SSFCKeditor04007941280106517 15&Toolbar=Default#_ftnref1)** Toxicity Characteristic Leaching Procedure – EPA Method 1311

More in Environmental Decisions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/default.htm)

Decisions for Food-Contact Notifications (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105897.htm)

Decisions for Petitions (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105895.htm)

Definitions of Environmental Terms (/Food/IngredientsPackagingLabeling/EnvironmentalDecisions/ucm105934.htm)

1. Date: September 7, 2015

2. Name of Applicant/Petitioner:

Pure Bioscience, Inc.
1725 Gillespie Way
El Cajon, CA 92020

3. Address:

Mitchell Cheeseman, Ph.D.
Steptoe & Johnson LLP
1330 Connecticut Ave. NW
Washington, DC 20036

4. Description of Proposed Action:

a. Requested Action

The action requested in this Notification is the establishment of a clearance to permit the use of a solution of silver dihydrogen citrate (SDC) stabilized with sodium lauryl sulfate and citric acid as an antimicrobial solution applied to fruits and vegetables intended to be processed.

b. Need for Action

SDC solutions reduce populations of microorganisms that may be present on fruits and vegetables and retards their spoilage by reducing the number of spoilage-causing organisms. SDC is expected to be an important preventive control in providing safer produce for consumers.

c. Locations of use/disposal

This product is for use in fruit and vegetable processing plants throughout the United States. The expected route of disposal for waste solution is either the processing plant wastewater treatment facility or a publically owned treatment works (POTW).

The antimicrobial will be applied by spray or dip to the surfaces of fruits and vegetables. After the diluted product is applied to the fruits and vegetables, the bulk of the solution drains off of the produce. The waste solution ultimately runs into drains and enters the processing plant water treatment facility or POTW. Very minor quantities are lost to evaporation into the air.

5. Identification of Substances that are the subject of the Proposed Action:

The raw materials used in this product are silver, citric acid, sodium lauryl sulfate, and water. The result of the reaction of silver and citric acid in the presence of SLS is to form an equilibrium stabilized complex of SDC. When the mixture is diluted for use on fruits and vegetables (1:80 or 1:160), the solution contains no more than 30 ppm silver as SDC.

Complete Name	CAS No.	Molecular Weight	Molecular Formula
Silver	7722-84-1	34.01	Ag
Citric acid	64-19-7	60.05	$C_6H_8O_7$
Sodium Lauryl Sulfate	79-21-0	76.05	$NaC_{12}H_{25}SO_4$
Water	7732-18-5	18.01	H_2O

6. Introduction of Substances into the Environment:

a. Introduction of substances into the environment as a result of manufacture:

The FCS is manufactured in plants which meet all applicable Federal, State and local environmental regulations. Pure Bioscience also asserts that there are no extraordinary circumstances pertaining to the manufacture of the FCS such as 1) unique emission circumstances are not adequately addressed by general or specific emission requirements (including occupational) promulgated by Federal, State or local environmental agencies and the emissions may harm the environment; 2) a proposed action threatens a violation of Federal, State or local environmental laws or requirements (40 CFR 1508.27(b)(10)); and 3) production associated with a proposed action may adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora to be endangered or threatened, or wild fauna or flora that are entitled to special protection under some other Federal law.

b. Introduction of substances into the environment as a result of use/disposal:

Introduction of dilute solutions of the product into the environment will take place primarily via release from wastewater treatment systems. Introduction of the components of the product into the environment will result from use of the product as an antimicrobial agent for spray or dip application onto fruits and vegetables and the subsequent disposal of such water and spray/dip drainage into the processing plant wastewater treatment facility or POTW. The total amount of product used at a typical facility can be estimated, although the actual amounts used will vary, depending on equipment used and the amount of produce processed.

Based on confidential market volume information, we have estimated that silver will be present at a concentration of 18 ppb in wastewater exiting a very large processing plant. We believe that such a plant is a worst case as it will likely have its own on site treatment and may discharge processed water directly to surface waters under its own NPDES permit. Alternatively much smaller plants might discharge water to a POTW. However other inflow for the POTW would further dilute silver and other residues.

Based on the same assumptions as silver, SLS will be present at a concentration of 180 ppb and citric acid will be present at a concentration of 1.5 ppm.

Treatment of the process water at the on-site wastewater treatment plant is expected to result in near complete biodegradation of the organic components of the SDC solution (citric acid, citrate and sodium lauryl sulfate). This expectation is based on the available data on the biodegradability of SLS[1] and citric acid[2] which indicates that these compounds will biodegrade by at least 96% and 97%, respectively, before entry into surface waters. If we assume that level of biodegradation and use a dilution factor of 1/10 for discharge to surface waters worst-case discharges of 4.5 µg/L for citric acid and 0.72 µg/L for SLS can be estimated.[3]

If we apply the estimate by Ratte et al. that > 94% of the silver will partition to sludge during treatment at the on-site facility[4] to the concentration exiting the processing facility (18 µg/L), then the EIC for silver in water released from the on-site treatment facility would be 1.1 µg/L and the concentration in sludge generated at the onsite treatment facility would be 16.9 µg/L, the terrestrial EEC.[5] With respect to silver partitioning to sludge, EPA's Reregistration Eligibility Decision (RED) document for silver concludes that silver partitioning to sludge during wastewater treatment will be in the form of silver sulfides.[6] The silver in the water released from the on-site treatment facility will be further diluted either because it is released to surface waters or processed in a POTW. In either case, the concentration of silver in the aquatic compartment will be further diluted 10-fold to produce an EEC of 110 ng/L.[7] The EECs for silver, SLS and citric acid are calculated below:

- $Silver_{(aq)}$: 18 µg/L * 6% partitioning to water = 1.1 µg/L (ppb)
  1.1 µg/L (ppt) ÷ 10 (dilution in POTW or surface water) = 110 ng/L
- $Silver_{(terr)}$: 18 µg/L (ppb) * 94% partitioning to sludge = 16.9 µg/L
- SLS: 180 µg/L (ppb) * 0.04 ÷ 10 = 720 ng/L [8]
- Citric acid: 1.5 mg/L (ppm) *.03 ÷ 10 = 4.5 µg/L[9]

For a produce plant discharging to a POTW we would expect the above concentrations to be reduced by 10-fold. Recovery of precious metals from sewage

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[1] OECD SIDS Assessment of Sodium Docecyl Sulfate, 1995, pg. 6.
[2] Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox. Environm. Safety 3: 159-173, 1979. See specifically Table 3 Page 165.
[3] Rapaport, Robert A., 1988. Prediction of consumer product chemical concentrations as a function of publically owned treatment works treatment type and riverine dilution. Environmental Toxicology and Chemistry, 7(2), 107-115. Found online at:
http://onlinelibrary.wiley.com/doi/10.1002/etc.5620070204/abstract.
[4] Ratte, Hans Toni, Bioaccumulation and toxicity of Silver Compounds: A Review, Environmental Toxicology and Chemistry, Vol. 18, no.1, pp 89-108 1999.(Specifically pg. 89)
[5] 18 µg/L * 6% = 1.1 µg/L ; 18 µg/L * 94% = 16.9 µg/L
[6] EPA Reregistration Eligibility Decision (RED) on Silver (1992) pg. 16. Available Online at:
http://www.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-75_5-Sep-07.pdf
[7] Op Cite Rapaport.
[8] We account for 96% degradation and 10-fold dilution.
[9] We account for 97% degradation and 10-fold dilution.

sludge may be important in reducing the environmental introductions of silver from the use of the additive. In our opinion, the anticipated daily use level of SDC would result in sufficient silver in sludge produced at an onsite treatment facility to make recovery of silver from the sludge economically viable. Therefore, we expect little or no introductions of silver into the terrestrial compartment, as it will be worthwhile for the user to transport sludge to a recovery facility or to build a recovery facility on site. We have included our estimates of recoverable silver for our example processing plant in a confidential attachment.

For produce plants discharging to a POTW, we expect the concentrations of silver and other components will be reduced by 10-fold by other intake into the POTW. Therefore we estimate that the terrestrial EEC for silver will be 10-fold lower than the above concentration or 1.7 µg/L. Moreover because of the typically large wastewater-loading rate of produce plants, we would expect that such plants would need to be covered by municipal and/or state permitting even if discharging to a POTW. We would further expect that such produce plants would need to report significant changes in effluent such as the silver in wastewater. Thus, POTWs will be able to make informed determinations regarding the viability of silver recovery from POTWs, the proper handling of sludge and effluent and any impacts on processing.

Pursuant to 40 CFR 261.24, silver is a toxic hazardous waste - carrying a waste code of D011 - if detected at 5 mg/L by Toxicity Characteristic Leaching Procedure (TCLP) - EPA Method 1311. Accordingly, if not sent for silver recovery, sludge containing more than 5 mg/L silver TCLP must be managed and disposed of as a hazardous waste. However, we have estimated a concentration of silver in sludge of 16.9 µg/L. This concentration is nearly 300-fold lower than the level requiring disposal of the sludge as toxic waste. Therefore, EPA's limits should be no issue with respect processing of the sludge for silver recovery or other purposes.

7. Fate of Emitted Components in the Environment:

Only silver sulfide and very minor amounts of silver ion, citric acid and SLS are expected to survive treatment at the on-site water treatment facilities at fruit and vegetable processing plants. We reference EPA's reregistration review[10] which considers LC_{50}s for freshwater fish, which range from 3.9 to 280 µg/L, LC_{50}s which are 3.5-240 times larger than the EEC for silver in water. In addition, EPA references EC_{50}s for freshwater invertebrates of 0.25 to 4500 µg/L, the lower value is 2.5-fold higher than our EEC for silver and the upper value is over 40,000 times larger. Finally, EPA references EC_{50}s for marine/estuarine invertebrates of between 5.8 and 150 µg/L, EC_{50}s that are, at a minimum, nearly 60-fold larger than our aquatic EEC. Thus, toxicity values for aquatic organisms exposed to silver indicate a margin of safety of at least 2.5-fold. Moreover, we would expect, as does EPA, that the discharge of silver from POTWs or onsite treatment facilities to surface waters will be insignificant regarding the concentration of silver ion

[10] Op Cite EPA ppg. 16-17.

in water. This belief is based on the physical properties and reactivity of silver with ions present in the water and soil contacting the water.[11]

We have estimated an EEC of 16.9 µg/L of silver for the terrestrial compartment and expect that this silver will be present as silver sulfides. The equivalent concentration of silver sulfide would be 38.8 µg/L. Ratte (1999) reports a NOEC for earthworms for silver sulfide in sludge of 62 mg Ag/Kg sludge.[12] If we assume a density of sludge of 1.5g/cm^3 this NOEC would translate to about ~41 mg/L, a value which would represent a margin of safety compared to our terrestrial EEC of ~ 1,000-fold.[13] This is a significant safety margin given that our estimate of silver concentration assumes sludge, which is not consigned for silver recovery, will not be diluted by other sludge if applied to agricultural or other lands. In addition, Ratte (1999) reports NOECs for multiple terrestrial plants of 771 mg/Kg (the highest level tested).[14] All of these referenced experiments demonstrate no toxic effect for silver sulfide in sewage sludge at exposure levels much higher than our worst-case estimates of EECs. Therefore, we conclude that the requested use of the FCS has no potential for environmental impact from increased introductions of silver.

Remaining citric acid[15] and SLS[16] concentrations would be expected to continue to biodegrade in the environment.

In the use scenario described above, waste antimicrobial solution (from application and drainage) will be directed to an on-site wastewater treatment facility. Water from such a facility will likely be discharged to surface waters. Alternatively, smaller facilities may discharge to a POTW with or without initial treatment. In addition, sludge from an onsite treatment facility is likely to be consigned for recovery of silver and other metals because of cost savings. Both water and sludge from a POTW is expected to have significantly lower silver concentrations based on dilution from other wastewater sources. Because of the volume of effluent generated in produce processing, we expect that any facility discharging to a POTW will require local or state permitting. This process should inform the POTW of the potential silver concentration. Thus, POTWs should be account for such concentrations and may also be able to consigned te resulting sludge for silver and metal recovery, if appropriate.

8. Environmental Effects of Released Substances:

Citric acid appears to be of low acute toxicity to fish, daphnia and algae.[17] The HERA project 2005 environmental risk assessment for citric acid derived a predicted no effect concentration (PNEC) of 0.8 mg/L based on toxicity data of sodium citrate on fish,

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[11] Ibid.
[12] Op Cite Ratte, pg. 97.
[13] Donahue, Roy Luther; Miller, Raymond W.; Shickluna, John C. (1977). Soils: An Introduction to Soils and Plant Growth. Prentice-Hall pg. 60. ISBN 0-13-821918-4.
[14] Op Cite Ratte pg. 98.
[15] Op Cite Gericke.
[16] Op Cite OECD
[17] Op Cite Gericke.

daphnia and algae.[18] This very conservative PNEC is nearly 200-fold above our worst case estimate of introductions (4.5 µg/L) for citric acid.

SLS also appears to be of low toxicity to aquatic organisms.[19] The OECD SIDS report references a lowest LOEC of 20 µg/L in Scenedesmus quadricauda. This LOEC is 30-fold larger than our worst case estimated level of introduction for SLS (720 ng/L) for the proposed use.

EPA has thoroughly considered the toxicity of silver processed in wastewater facilities and concluded that no significant environmental risk of aquatic toxicity exists.[20] Moreover, the same EPA evaluation argues that the insoluble nature of silver sulfides will immobilize the vast majority of silver reducing toxic potential. We have estimated EECs for silver in the aquatic environment (110 ng/L) and in the terrestrial environment (16.9 µg/L silver, 38.3 µg/L silver sulfide).

As discussed above, ecotoxicity testing results of silver and silver compounds in aquatic environments and silver sulfide in terrestrial environments establish an acceptable margin of safety above our EECs for the aquatic and terrestrial compartments. Based on all of the above we conclude that approval of this food contact notification will not have any significant impact on the environment.

9. Use of Resources and Energy

The use of the Pure Bioscience product will not require additional energy resources for treatment and disposal of waste solution, as the components are adequately dealt with through existing infrastructure. The raw materials used in the production of the mixture are commercially manufactured materials that are produced for use in a variety of chemical reactions and production processes. Energy used specifically for the production of the mixture components is not significant.

10. Mitigation Measures

As discussed above, no significant adverse environmental impacts are expected to result from the use and disposal of the dilutions of antimicrobial product. Existing mitigation measures, which address potential environmental risk, include local permitting for large volume discharge to POTWs. In addition, Pure Bioscience intends to inform its customers regarding the potential cost recovery from extracting silver from sludge. Therefore, the use of the subject mixture is not reasonably expected to result in any environmental problem requiring additional mitigation measures of any kind.

[18] HERA, 2005, Substance: Citric Acid and Salts (CAS # 77-92-9; 5949-29-1; 6132-04-3).
[19] Op Cite OECD SIDS Assessment of Sodium Lauryl Sulfate 1995, ppg. 21-23.
[20] Op Cite EPA 1992, pg. 16-17.

11. Alternatives to the Proposed Action

No potential adverse environmental effects are identified herein that would necessitate alternative actions to that proposed in this Food Contact Notification. If the proposed action is not approved, the result would be the continued use of the currently marketed antimicrobials that the subject FCS would replace. Such action would have no environmental impacts. The addition of the antimicrobial to the options available to produce processors is not expected to increase the use of such antimicrobials.

12. List of Preparers

Dr. Mitchell Cheeseman, Steptoe & Johnson LLP, 1330 Connecticut Ave. NW, Washington DC, 20036

Dr. Cheeseman holds a Ph.D. in Chemistry from the University of Florida. Dr. Cheeseman served for 18 months as a NEPA reviewer in FDA's food additive program. He has participated in FDA's NEPA review of nearly 800 food additive and food contact substance authorizations and he supervised NEPA review for FDA's Center for Food Safety and Applied Nutrition for five and a half years from 2006 to 2011 including oversight of FDA's initial NEPA review for the regulations implementing the Food Safety Modernization Act.

13. Certification

The undersigned official certifies that the information provided herein is true, accurate, and complete to the best of his knowledge.

Date: September 7, 2015

Mitchell Cheeseman

14. References

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Water Efficiency, Industry Specific Processes: Fruit and Vegetable Processing, North Carolina Division of Pollution Prevention and Environmental Assistance, May 2009.

Attachment 8

Comprehensive Toxicological Profile for Silver

The toxicity of silver and silver salts has been reviewed extensively by multiple independent and government bodies because of its natural presence in the environment, its industrial production and use as well as its growing use as an antimicrobial. FDA has reviewed the safety of its use in food contact materials and as an antimicrobial in the treatment of poultry and fresh fruits and vegetables. We have performed a comprehensive search of the available literature to identify any additional studies not included in previous reviews. Relevant reviews and studies are included in Attachment 6 of this FCN.

The safety of silver has been thoroughly reviewed multiple times by several U.S. Federal Agencies. Most recently the U.S. Environmental Protection Agency (EPA) established an exemption from the requirement for a pesticide tolerance for silver from silver dihydrogen citrate antimicrobials (the FCS) of 50 ppm in hard surface sanitizing solutions.[1] That tolerance was based in part on EPA's chronic dietary reference dose (CDRfD) of 1 µg/Kg-bw-d. Thus EPA's tolerance determination and the underlying safety determination establish a safe human exposure of 60 µg/p-d. EPA's CDRfD is primarily based on the results of a human biomonitoring study conducted by Gaul and Staud in 1935 and measurements of argyria in participants.[2] It should be noted that this endpoint is cosmetic and is not related to systemic toxicity or toxicity with respect to the skin. In the 1935 study by Gaul and Staud, silver was administered for medicinal purposes to 70 patients for periods from 2 to 9 years. Of the 70 patients receiving medicinal silver, only 1 in 70 developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 14µg/Kg-bw-d and was considered by EPA as the lowest observed effect level. Other patients in the study did not develop argyria until doses five times higher were administered.

In addition, the EPA assessment considers a 2002 NTP study in rats of orally administered silver acetate for potential developmental toxicity.[3] In the NTP study, three groups of 25 female Sprague Dawley rats were dosed with 10, 30, or 100 mg/Kg-d silver acetate from gestational day 6 to gestational day 19. Maternal feed and water consumption was reduced at the mid-dose which was subsequently designated as the LOAEL. The maternal NOAEL for silver acetate was determined to be 10 mg/Kg-d (6.5 mg/Kg-d silver). The NOAEL for silver acetate was determined to be 100 mg/Kg-d (64.6 mg/Kg-d silver) based on the absence of any biologically or statistically significant developmental toxicity effects.

Finally, EPA considered the pharmacokinetics of silver in relation to the above toxicity data. The EPA review cites a 90% first-pass removal rate as silver is taken up through the GI tract and processed by the liver and eliminated in the feces. EPA states that the remaining 10% that is not eliminated in the feces, reacts with proteins by binding to a specific chemical group contained in the structure of the protein. By forming silver-protein complexes through this

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[1] EPA (2009) Residues of Silver in Foods from Food Contact Surface Sanitizing Solutions; Exemption from the Requirement of aTolerance, 74 FR 27447-454.

[2] Gaul LE, Staud AH. Clinical spectroscopy. Seventy cases of generalized argyrosis following organic and colloidal silver medication. Journal of the American Medical Association, 1935, 104:1387-1390.

[3] NTP (2002) Final Study Report: Developmental Toxicity Evaluation for Silver Acetate (CAS Reg. No. 563-63-3) National Toxicology Program.

binding action, the remaining silver is removed from circulation. This remaining fraction accounts for the background levels of silver that are found within the body. EPA notes that only at excessive doses, doses far higher than anticipated here do the pathways of elimination become saturated and deposition of these complexes in the tissues is increased. The formation of these complexes and deposition in the skin, mucous membranes, and conjunctiva is the primary mechanism which results in the development of argyria. The estimated daily intake anticipated here is many times lower than LOAELs and NOELs derived by EPA.

The World Health Organization also reviewed the toxicity of silver in drinking water in 1996.[4] WHO concluded that a lifetime exposure of 10 grams of silver could be considered a human no observable effect level. For a human lifespan of 70 years this lifetime dosage equates to an average of about 390µg/p-d or about 6.5µg/Kg-bw-d. WHO also notes that typical consumer exposure from drinking water is significantly below this level. The Agency for Toxic Substances and Disease Registry (ATSDR) also reviewed the toxicity of silver in 1990.[5] ATSDR comes to substantially the same conclusions as EPA based on substantially the same data. Finally, we are aware that FDA's authorization of silver in food contact materials and antimicrobial applications is also based largely on the data reviewed by EPA and ATSDR.

FDA has also reviewed the toxicity of silver ion numerous times regarding submission under its food contact notification program over the past 14 years. In particular, FDA reviewed the toxicity of silver ion produced by the addition of silver nitrate to water used in the processing of poultry under FCN 296. Our inquiry to FDA regarding the EDI from the use authorized under FCN 296 resulted in an email which informed us that the EDI from that use was 4µg/Kg food or 12µg/p-d.

Our EDI of silver ion from our intended use at 30 ppm is 5.8µg/p-d (0.1µg/Kg-bw-d).[6] Moreover, the intended use of SDC is substitutional for the use authorized in FCN 296 as an antimicrobial on poultry carcasses. In addition, we are requesting a use only in spray on the surface of poultry or poultry dips and not in chiller baths. In addition, we are specifying that SDC will not be used in combination with any other silver antimicrobial in spray or baths. Thus, authorization of our intended use of SDC will not increase consumer exposure to silver ion.

We are aware that FDA has more recently reviewed a 2-generation reproduction and fertility study believed relevant to silver consumption.[7] Although FDA's review was not able to confirm an acceptable daily intake based on the lowest dose level in the study (3.9 mg/Kg-bw-d) we note that this dose level which was not associated with the effect(s) noted at higher dosages is more than 39,000-fold higher than our EDI of 0.1 µg/Kg-bw-d. Thus, we respectfully submit that a sufficient margin of safety also exists for the effects of concern in FDA's June 30, 2004 memorandum.

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[4] WHO (2003) Silver in Drinking-water; Background document for development of WHO Guidelines for Drinking-water Quality (WHO/SDE/WSH/03.04/14).

[5] ATSDR (1990). Toxicological Profile for Silver. Agency for Toxic Substances and Disease Registry U.S. Public Health Service.

[6] For a 60 Kg adult.

[7] FDA Memorandum dated June 30, 2004, from Andrew J. McDougal, Ph.D. to Elizabeth Sanchez, Ph.D. (redacted)

Comprehensive Toxicological Profile of Sodium Lauryl Sulfate (SLS)

Sodium lauryl sulfate (CAS Reg. No. 151-21-3) is a surfactant, widely used in a variety of commercial products including cleaners, hard surface sanitizers and other antimicrobials. In addition, SLS is permitted for a wide variety of uses. The safety of SLS has been thoroughly considered by the Environmental Protection Agency[1] and has been the subject of other peer reviewed safety assessments.[2]

The most recent review of the safety of SLS was EPA's 2009 review. In that review EPA considered a wide variety of available toxicity data and derived a point of departure for chronic risk assessments for SLS of 100 mg/Kg-bw-d. In addition, EPA states that "Sodium lauryl sulfate was negative in tests for genotoxicity, including in vitro bacterial reversion mutation assays (Ames test), mammalian bone marrow chromosome aberration tests, mammalian erythrocyte micronucleus tests, and rodent dominant lethal mutation assays." The lack of mutagenic activity for anionic surfactants is also supported in the published scientific literature (Yam, Bomman et al., 1984). Moreover, EPA emphasizes, as does the HERA (2002) risk assessment, the lack of any structural feature that would suggest mutagenic potential.

As discussed by EPA, the repeated dose toxicity data on alkyl sulfates including sodium lauryl sulfate demonstrate effects consistent with surfactant-mediated irritant effects. The common target organs of toxicity following repeated-dose oral exposure are the forestomach in gavage studies, and the liver and kidneys in dietary studies. EPA references the available chronic toxicity testing data on SLS and points to the lack of any treatment related effects at doses below 100 mg/kg-bw-d.

EPA also reports that there is no evidence of increased susceptibility to the offspring of rats, rabbits, and mice following prenatal or postnatal exposure to sodium lauryl sulfate. EPA references a developmental toxicity study with sodium lauryl sulfate in rats, rabbits and mice, in which maternal toxicity manifested primarily as decreased body weight gain, and developmental toxicity manifested as reduction in pup viability, post-implantation loss, and reduced litter weight (all of which occurred in mice but not rats and rabbits) at a dose level of 600 mg/kg/day. EPA reports a NOAEL for maternal and developmental effects in that study of 300 mg/kg/day. EPA also states that there was no evidence of neurotoxicity in the adult animals. Finally EPA references a 2-generation reproductive toxicity study conducted with a related chemical, alpha-alkyl (C12) olefin sulfonate, showed no treatment-related adverse reproductive effects and no adverse histopathological effects on systemic organs at dose levels up to 285mg/kg/day.

EPA also acknowledges that the metabolism and toxic mode of action for SLS is well understood. Both EPA and HERA reviews note the similarity in toxicity among alkyl sulfates, which can be related to their mechanisms of action and common pathways of metabolism. EPA states that surfactants such as sodium lauryl sulfate can damage the structural integrity of cellular membranes at high dose levels. Thus, surfactants are often corrosive and irritating in concentrated solutions. EPA agrees with the likelihood expressed in the HERA review that some

[1] EPA (2009) Memorandum dated August 9, 2009, Sodium Lauryl Sulfate, Human Health Risk Assessment to Support proposed Exemption from the Requirement of a Tolerance When Used as an Inert Ingredient in Pesticide Formulations. From Kerry B. Leifer to PV Shah.

[2] HERA (2002) Available at: http://www.heraproject.com/RiskAssessment.cfm

of the observed toxicity seen in the repeated studies, such as irritation of forestomach or decreased body weight gain, can be attributed to the corrosive and irritating nature of these surfactants. In addition, EPA states that alkyl sulfates are extensively metabolized in mammals with the predominant metabolite being the short-chained, 4-carbon sulfate ester, butyric acid 4-sulfate which is highly polar and excreted rapidly in the urine.

The HERA review specifically references a published developmental toxicity study assessed the teratogenic potential of AS in rats, mice and rabbits following oral (gavage) administration (Palmer et al, 1975 a b).[3,4] The dose range in this study was 0, 0.2, 2, 300 and 600 mg/kg/day and the protocol was comparable to OECD 414 guidelines. The HERA review notes that the chain length of the alkyl sulfates evaluated for teratogenicity was not specified in the study report but expresses the belief that the compound is the C_{12} sodium salt, most commonly used as a surrogate for the category. In the study, mice and rabbits were more sensitive to maternal toxicity induced by the test material. HERA reports that at the 600 mg/kg dose, marked maternal toxicity was evident in mice and rabbits, while slight to moderate toxicity was observed in rats at the same dose. In addition, an increased incidence of total litter loss occurred at doses that caused frank maternal toxicity; when dams showing total litter loss were excluded from the analysis, litter parameters were unchanged by treatment. In mice, a higher incidence of minor skeletal anomalies occurred at 600 mg/kg of alkyl sulfates, however, in all species, the incidence of major or minor visceral or skeletal anomalies was unaffected by treatment at non-maternally toxic doses. HERA reports that the NOEL for maternal toxicity for all species was 2 mg/kg/day; for litter and pregnancy data a NOEL of 2 mg/kg/day was established. For fetal data and NOEL of 600 mg/kg/day was observed for rats; in rabbits and mice the NOEL was 300 mg/kg/day. The HERA report reasons that the spread in the dose levels selected for this study resulted in an apparent low NOEL for maternal and litter effects; however the severity of the effects at 300 mg/k/day suggested that the true NOEL for these effects is between 2 and 300 mg/kg.

Conclusion

Based on the above referenced data, EPA arrives at a NOAEL of 100 mg/kg-bw-d and HERA arrives at a value of 60 mg/Kg-bw-d. Both of these values establish a margin of safety of much greater than 100,000 when compared to our EDI of 12 µg/p-d. Given the fact that the available data has established in previous reviews that SLS is not mutagenic, we respectfully submit that potential dietary exposures from our intended use of SLS are safe. Although FDA has not published a cumulative dietary intake (CEDI) for SLS based on existing authorizations we believe that authorization of the FCS would leave the CEDI effectively unchanged.

[3] Palmer AK, Readshaw MA et al. (1975a). Assessment of the Teratogenic Potential of Surfactants. Part I-Las, AS and CLD. Toxicology 3(1): 91-106.
[4] Palmer AK, Readshaw MA et al. (1975b). Assessment of the Teratogenic Potential of Surfactants. Part II-AOS. Toxicology 3(1): 107-13.

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The safety of silver has been thoroughly reviewed multiple times by several U.S. Federal Agencies. Most recently the U.S. Environmental Protection Agency (EPA) established an exemption from the requirement for a pesticide tolerance for silver from silver dihydrogen citrate antimicrobials (the FCS) of 50 ppm in hard surface sanitizing solutions.[1] That tolerance was based in part on EPA's chronic dietary reference dose (CDRfD) of 1 µg/Kg-bw-d. Thus EPA's tolerance determination and the underlying safety determination establish a safe human exposure of 60 µg/p-d. EPA's CDRfD is primarily based on the results of a human biomonitoring study conducted by Gaul and Staud in 1935 and measurements of argyria in participants.[2] It should be noted that this endpoint is cosmetic and is not related to systemic toxicity or toxicity with respect to the skin. In the 1935 study by Gaul and Staud, silver was administered for medicinal purposes to 70 patients for periods from 2 to 9 years. Of the 70 patients receiving medicinal silver, only 1 in 70 developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 14µg/Kg-bw-d and was considered by EPA as the lowest observed effect level. Other patients in the study did not develop argyria until doses five times higher were administered.

In addition, the EPA assessment considers a 2002 NTP study in rats of orally administered silver acetate for potential developmental toxicity.[3] In the NTP study, three groups of 25 female Sprague Dawley rats were dosed with 10, 30, or 100 mg/Kg-d silver acetate from gestational day 6 to gestational day 19. Maternal feed and water consumption was reduced at the mid-dose which was subsequently designated as the LOAEL. The maternal NOAEL for silver acetate was determined to be 10 mg/Kg-d (6.5 mg/Kg-d silver). The NOAEL for silver acetate was determined to be 100 mg/Kg-d (64.6 mg/Kg-d silver) based on the absence of any biologically or statistically significant developmental toxicity effects.

Finally, EPA considered the pharmacokinetics of silver in relation to the above toxicity data. The EPA review cites a 90% first-pass removal rate as silver is taken up through the GI tract and processed by the liver and eliminated in the feces. EPA states that the remaining 10% that is not eliminated in the feces, reacts with proteins by binding to a specific chemical group contained in the structure of the protein. By forming silver-protein complexes through this

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[3] NTP (2002) Final Study Report: Developmental Toxicity Evaluation for Silver Acetate (CAS Reg. No. 563-63-3) National Toxicology Program.

binding action, the remaining silver is removed from circulation. This remaining fraction accounts for the background levels of silver that are found within the body. EPA notes that only at excessive doses, doses far higher than anticipated here, do the pathways of elimination become saturated and deposition of these complexes in the tissues is increased. The formation of these complexes and deposition in the skin, mucous membranes, and conjunctiva is the primary mechanism which results in the development of argyria. The estimated daily intake anticipated here is many times lower than LOAELs and NOELs derived by EPA.

The World Health Organization also reviewed the toxicity of silver in drinking water in 1996.[4] WHO concluded that a lifetime exposure of 10 grams of silver could be considered a human no observable effect level. For a human lifespan of 70 years this lifetime dosage equates to an average of about 390 µg/p-d or about 6.5 µg/Kg-bw-d. WHO also notes that typical consumer exposure from drinking water is significantly below this level. The Agency for Toxic Substances and Disease Registry (ATSDR) also reviewed the toxicity of silver in 1990.[5] ATSDR comes to substantially the same conclusions as EPA based on substantially the same data. Finally, we note that the European Union Scientific Committee on Consumer Safety (SCCS) has reviewed the safety of combined citric acid and silver citrate products similar or identical to the FCS.[6] The SCCS review established a NOAEL of 1000 mg/Kg-bw-d for silver citrate products similar or identical to SDC. This NOAEL is over 6 orders of magnitude larger than our cumulative estimated daily intake below.

FDA has also reviewed the toxicity of silver ions numerous times regarding submission under its food contact notification program over the past 14 years. In particular, FDA reviewed the toxicity of silver ion produced by the addition of silver nitrate to water used in the processing of poultry under FCN 296. Our inquiry to FDA regarding the EDI from the use authorized under FCN 296 resulted in an email which informed us that the EDI from that use was 4 µg/Kg food or 12 µg/p-d.

Our EDI of silver ion from our previously requested use at 30 ppm in processing poultry is 5.0 µg/p-d (0.083µg/Kg-bw-d).[7] The EDI for silver ion from our requested use on fruits and vegetables is estimated to be 6.72 µg/p-d (0.112 µg/Kg-bw-d) resulting in a combined EDI for all uses of 11.72 µg/p-d (0.195µg/Kg-bw-d). Moreover, the combined intended uses of SDC is substitutional for the use authorized in FCN 296 as an antimicrobial on poultry carcasses, fruits and vegetables. Thus, authorization of our intended use of SDC will not increase consumer exposure to silver ion.

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[4] WHO (2003) Silver in Drinking-water; Background document for development of WHO Guidelines for Drinking-water Quality (WHO/SDE/WSH/03.04/14).

[5] ATSDR (1990). Toxicological Profile for Silver. Agency for Toxic Substances and Disease Registry U.S. Public Health Service.

[6] Scientific Committee on Consumer Safety (SCCS), Opinion on Citric Acid and Silver Citrate 13, October, 2009. SCCS/1274/09

[7] For a 60 Kg adult.

We are aware that FDA has more recently reviewed a 2-generation reproduction and fertility study believed relevant to silver consumption.[8] Although FDA's review was not able to confirm an acceptable daily intake based on the lowest dose level in the study (3.9 mg/Kg-bw-d) we note that this dose level which was not associated with the effect(s) noted at higher dosages is more than ~20,000-fold higher than our cumulative EDI of 0.195 µg/Kg-bw-d. Thus, we respectfully submit that a sufficient margin of safety also exists for the effects of concern in FDA's June 30, 2004 memorandum.

[8] FDA Memorandum dated June 30, 2004, from Andrew J. McDougal, Ph.D. to Elizabeth Sanchez, Ph.D. (redacted)

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The most recent review of the safety of SLS was EPA's 2009 review. In that review EPA considered a wide variety of available toxicity data and derived a point of departure for chronic risk assessments for SLS of 100 mg/Kg-bw-d. In addition, EPA states that "Sodium lauryl sulfate was negative in tests for genotoxicity, including in vitro bacterial reversion mutation assays (Ames test), mammalian bone marrow chromosome aberration tests, mammalian erythrocyte micronucleus tests, and rodent dominant lethal mutation assays." The lack of mutagenic activity for anionic surfactants is also supported in the published scientific literature (Yam, Bomman et al., 1984). Moreover, EPA emphasizes, as does the HERA (2002) risk assessment, the lack of any structural feature that would suggest mutagenic potential.

As discussed by EPA, the repeated dose toxicity data on alkyl sulfates including sodium lauryl sulfate demonstrate effects consistent with surfactant-mediated irritant effects. The common target organs of toxicity following repeated-dose oral exposure are the forestomach in gavage studies, and the liver and kidneys in dietary studies. EPA references the available chronic toxicity testing data on SLS and points to the lack of any treatment related effects at doses below 100 mg/kg-bw-d.

EPA also reports that there is no evidence of increased susceptibility to the offspring of rats, rabbits, and mice following prenatal or postnatal exposure to sodium lauryl sulfate. EPA references a developmental toxicity study with sodium lauryl sulfate in rats, rabbits and mice, in which maternal toxicity manifested primarily as decreased body weight gain, and developmental toxicity manifested as reduction in pup viability, post-implantation loss, and reduced litter weight (all of which occurred in mice but not rats and rabbits) at a dose level of 600 mg/kg/day. EPA reports a NOAEL for maternal and developmental effects in that study of 300 mg/kg/day. EPA also states that there was no evidence of neurotoxicity in the adult animals. Finally EPA references a 2-generation reproductive toxicity study conducted with a related chemical, alpha-alkyl (C12) olefin sulfonate, showed no treatment-related adverse reproductive effects and no adverse histopathological effects on systemic organs at dose levels up to 285mg/kg/day.

EPA also acknowledges that the metabolism and toxic mode of action for SLS is well understood. Both EPA and HERA reviews note the similarity in toxicity among alkyl sulfates, which can be related to their mechanisms of action and common pathways of metabolism. EPA states that surfactants such as sodium lauryl sulfate can damage the structural integrity of cellular membranes at high dose levels. Thus, surfactants are often corrosive and irritating in concentrated solutions. EPA agrees with the likelihood expressed in the HERA review that some

[1] EPA (2009) Memorandum dated August 9, 2009, Sodium Lauryl Sulfate, Human Health Risk Assessment to Support proposed Exemption from the Requirement of a Tolerance When Used as an Inert Ingredient in Pesticide Formulations. From Kerry B. Leifer to PV Shah.

[2] HERA (2002) Available at: http://www.heraproject.com/RiskAssessment.cfm

of the observed toxicity seen in the repeated studies, such as irritation of forestomach or decreased body weight gain, can be attributed to the corrosive and irritating nature of these surfactants. In addition, EPA states that alkyl sulfates are extensively metabolized in mammals with the predominant metabolite being the short-chained, 4-carbon sulfate ester, butyric acid 4-sulfate which is highly polar and excreted rapidly in the urine.

The HERA review specifically references a published developmental toxicity study which assessed the teratogenic potential of SLS in rats, mice and rabbits following oral (gavage) administration (Palmer et al, 1975 a b).[3,4] The dose range in this study was 0, 0.2, 2, 300 and 600 mg/kg/day and the protocol was comparable to OECD 414 guidelines. The HERA review notes that the chain length of the alkyl sulfates evaluated for teratogenicity was not specified in the study report but expresses the belief that the compound is the C_{12} sodium salt, most commonly used as a surrogate for the category. In the study, mice and rabbits were more sensitive to maternal toxicity induced by the test material. HERA reports that at the 600 mg/kg dose, marked maternal toxicity was evident in mice and rabbits and slight to moderate toxicity was observed in rats at the same dose. In addition, an increased incidence of total litter loss occurred at doses that caused frank maternal toxicity; when dams showing total litter loss were excluded from the analysis, litter parameters were unchanged by treatment. In mice, a higher incidence of minor skeletal anomalies occurred at 600 mg/kg of alkyl sulfates, however, in all species, the incidence of major or minor visceral or skeletal anomalies was unaffected by treatment at non-maternally toxic doses. HERA reports that the NOEL for maternal toxicity for all species was 2 mg/kg/day; for litter and pregnancy data a NOEL of 2 mg/kg/day was established. For fetal data and NOEL of 600 mg/kg/day was observed for rats; in rabbits and mice the NOEL was 300 mg/kg/day. The HERA report reasons that the spread in the dose levels selected for this study resulted in an apparent low NOEL for maternal and litter effects; however the severity of the effects at 300 mg/k/day suggested that the true NOEL for these effects is between 2 and 300 mg/kg.

Conclusion

Based on the above referenced data, EPA arrives at a NOAEL of 100 mg/kg-bw-d and HERA arrives at a value of 60 mg/Kg-bw-d. Both of these values establish a margin of safety of much greater than 80,000 when compared to our cumulative EDI of 43.6µg/p-d.[5] Given the fact that the available data has established in previous reviews that SLS is not mutagenic, we respectfully submit that potential dietary exposures from our intended use of SLS are safe. Although FDA has not published a cumulative dietary intake (CEDI) for SLS based on existing authorizations we believe that authorization of the FCS would leave the CEDI effectively unchanged.

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[3] Palmer AK, Readshaw MA et al. (1975a). Assessment of the Teratogenic Potential of Surfactants. Part I-Las, AS and CLD. Toxicology 3(1): 91-106.

[4] Palmer AK, Readshaw MA et al. (1975b). Assessment of the Teratogenic Potential of Surfactants. Part II-AOS. Toxicology 3(1): 107-13.

[5] We have previously estimated an EDI for SLS from SDC use in poultry treatment of 11.9 µg/p-d. The cumulative EDI covers the current use and our previously requested use in poultry processing.

Attachment 9

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: June 4, 2009

SUBJECT: **Silver, Silver salts, and Silver Zeolites: *Human Health Assessment*** Scoping Document in Support of Registration Review.

RR Case Name	PC Codes	CAS #
Silver	072501	7440-22-4
Silver sulfate	072511	10294-26-5
Silver nitrate	072503	7761-88-8
Silver chloride	072506	7783-90-6
Silver oxide	129097	155645-89-9
Silver/Na../Zr Phosphate	072560	265647-11-8
Silver Zeolite	221700	130328-19-7

RR Case Nos.: 4082 and 5015

FROM: Timothy F. McMahon, Ph.D.
Senior Toxicologist/Risk Assessor
Antimicrobials Division 7510P

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Executive Summary

Silver and silver compounds, including metallic silver, silver salts (such as silver nitrate, silver chloride, etc.), and zeolite-based silver compounds (such as silver-copper zeolite, silver-zinc zeolite, and silver sodium hydrogen zirconium phosphate), have antimicrobial applications as algaecides, bacteriocides, bacteriostats, disinfectants, fungicides, sanitizers, virucides, and water purifiers. These compounds have a variety of use sites, including medical premises and equipment, human drinking water systems, materials preservatives, swimming pool algaecides, drinking water filters, fibers, textiles, spas, hot tubs, and whirlpools. Silver zeolites (silver-zinc zeolite, silver-copper zeolite, and silver sodium hydrogen zirconium phosphate) have applications as materials preservatives in plastic film, paint, paper coatings, adhesives, synthetic fibers, pigments, and textile finishing and manufacturing. Uses in heating, ventilation, and air conditioning systems (HVAC) as well as indirect food use applications (human drinking water contact articles such as water filter components, ice machine trays, water bottles, cups, and water storage vessels; and indirect food uses including packaging, gaskets, sponges, tiles, dishes, conveyor belts, food trays, general purpose containers, food processing equipment, and beverage processing equipment) are also noted for silver zeolite compounds. The Food and Drug Administration lists silver under 21 CFR 176.300 for use as a slimicide in the manufacture of paper and paperboard that contact food, with no stated limitation.

The Agency published a Reregistration Eligibility Decision document (RED) for silver and silver salts in 1993. That document only assessed the uses of silver in drinking water filters and swimming pools. At that time, the RED concluded that all products containing silver as the active ingredient for the uses mentioned were eligible for reregistration and new mammalian toxicology studies were not required. Toxicity of silver was assessed on the basis of open scientific literature studies conducted from the 1960's to 1980's. These studies reported effects of silver from repeated oral administration that included accumulation in kidney, increased weight of the left ventricle, and accumulation in specific areas of the brain. Mutagenicity testing showed negative results. Although these effects have been reported, the Agency has established regulatory limits for exposure to silver on the basis of argyria, an irreversible pigmentation of the skin and/or eyes occurring from systemic or dermal exposure to silver. Argyria is not currently considered a toxicologic effect in humans.

The Antimicrobials Division concluded that chemically, zeolite-based silver compounds are not similar to silver or silver salts and that at this time, a single toxicity database does not represent this class of chemicals as a whole. Each silver zeolite compound is thus considered separately for hazard and risk assessments, and bridging of toxicology data from one silver zeolite compound to another has not been addressed by either the Agency or registrants. Data that are available for the various silver zeolite compounds show effects including effects in liver, alterations in hematology, decreased thymus weight, and general systemic effects (e.g., decreased body weight). Testing for mutagenicity shows largely negative results.

From review of the available data, uses, and assessments, the division concludes that additional toxicity and exposure data are required for silver and zeolite-based silver compounds. For silver and silver salts, a repeat dose inhalation toxicity study is needed to address hazard and dose-

response from exposure to silver aerosols as is expected from uses such as the disinfectant spray uses. To address hazard and exposure from HVAC and indirect food uses of zeolite-based silver compounds, data needs may include assessment of developmental toxicity, inhalation toxicity, and reproductive toxicity. Specific data needs will be based on the specific zeolite-based compound. For example, silver sodium hydrogen zirconium phosphate has a toxicity database that is adequate for assessment of hazard based on its use pattern with the exception of a repeat dose inhalation toxicity study. The toxicity databases for silver copper and silver zinc zeolites are not as complete. Developmental toxicity data are not available for silver zinc zeolite, and reproductive toxicity data are not available for either silver copper or silver zinc zeolite. Subchronic (90-day) toxicity data are not available for silver zinc zeolite.

The dietary exposure database will require updating to support the registration review of silver/silver salts and zeolite-based silver compounds. Residential exposures to silver compounds via dermal, inhalation, and incidental oral routes can occur, and a revised exposure assessment may be needed. An aggregate assessment may also need to be considered depending on the outcome of toxicological endpoints selected for oral, dermal, and inhalation routes.

1. Introduction

The Antimicrobials Division (AD) Registration Review Team has evaluated the status of the human health assessments for silver, silver salts, and silver zeolites . Included in this registration review are two cases: Case 4082, which includes silver salts [silver (072501), silver nitrate (072503), silver chloride (072506), silver sulfate (072511), silver oxide (129097), and zeolite-based silver compounds (221700]; and Case 5015, silver sodium zirconium hydrogen phosphate (072560). For purposes of human health assessment, AD considered that silver and silver salts could be considered together, while zeolite-based silver compounds represented a different class and are not included with silver salts. Therefore, hazard databases are separate for silver salts and for zeolite-based silver compounds.

Registrations exist within the Antimicrobials Division (AD) of the Office of Pesticide Programs (OPP) for several types of silver-based pesticidal active ingredients, including registrations or proposed registrations for metallic silver, silver salts (such as silver nitrate, silver chloride, etc.), and zeolite-based silver compounds (such as silver-copper zeolite, silver-zinc zeolite, and silver sodium hydrogen zirconium phosphate. Antimicrobial use sites for silver include medical premises and equipment, human drinking water systems, materials preservatives, and swimming pools. For silver nitrate, use sites include drinking water filters and swimming pools. For silver chloride, use sites include fibers and textiles and swimming pools. Silver oxide use sites include spas, hot tubs, whirlpools, and pools. Silver sodium hydrogen zirconium phosphate and other zeolite-based silver compounds have uses as a materials preservative in plastic film, paint, paper coatings, adhesives, synthetic fibers, pigments, and textile finishing and manufacturing. Indirect food contact uses are also included.

Chemical Identities

Table 1a. Chemical Identity	
Common Name	Silver
CAS name	Silver
PC Code	072501
CAS registry number	7440-22-4
Registration Review Case No.	4082
Empirical Formula	Ag
Structure	

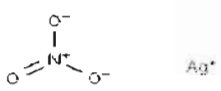
Table 1b. Chemical Identity	
Common Name	Silver Nitrate
CAS name	Silver Nitrate
PC Code	072503
CAS registry number	7761-88-8
Registration Review Case No.	4099
Empirical Formula	$AgNO_3$
Structure	

Table 1c. Chemical Identity	
Common Name	Silver Chloride
CAS name	Silver Chloride
PC Code	072506
CAS registry number	7783-90-6
Registration Review Case No.	4082
Empirical Formula	AgCl
Structure	

Table 1d. Chemical Identity	
Common Name	Silver Oxide
CAS name	Silver Oxide
PC Code	129097
CAS registry number	20667-12-3
Registration Review Case No.	4082
Empirical Formula	Ag_2O
Structure	Ag^+ Ag^+ O^{-2}

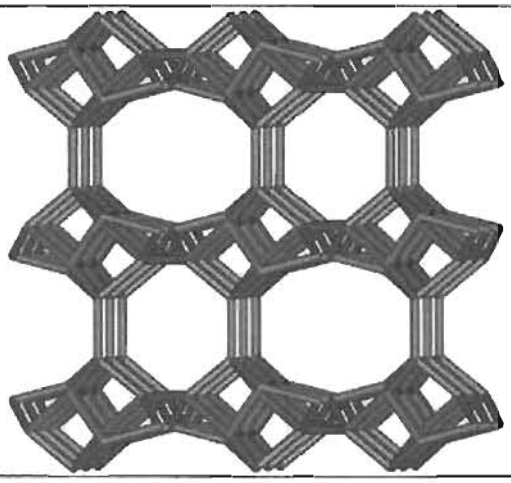
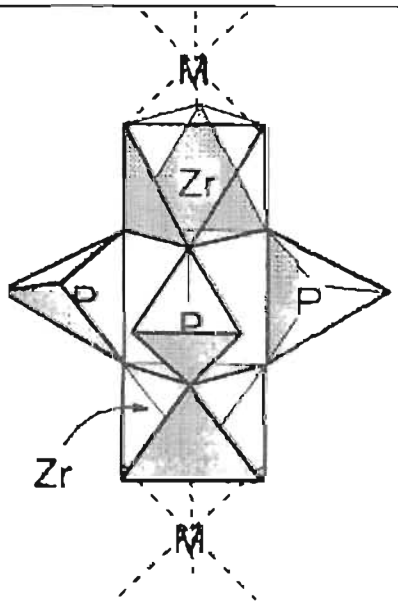
Table 1e. Chemical Identity	
Common Name	Silver Zeolite
CAS name	Silver Zeolite
PC Code	221700
CAS registry number	130328-19-7
Registration Review Case No.	4082
Empirical Formula	Cannot be determined
Structure	

Table 1f. Chemical Identity	
Common Name	Silver Sulfate
CAS name	Silver Sulfate
PC Code	072511
CAS registry number	10294-26-5
Registration Review Case No.	4082
Empirical Formula	Ag_2SO_4
Structure	Ag^+ SO_4^{-2} Ag^+

Table 1g. Chemical Identity	
Common Name	Silver sodium zirconium hydrogen phosphate
CAS name	Silver sodium zirconium hydrogen phosphate
PC Code	072560
CAS registry number	265647-11-8
Registration Review Case No.	4082
Empirical Formula (general)	$Ag_{(0.1-0.5)}Na_{(0.1-0.8)}H_{(0.1-0.8)}Zr_2(PO_4)_3$
Structure	 **Unit Cell Bonded to M**

2. Hazard Identification/Toxicology

2.1 Silver and Silver salts

Acute Toxicity

As noted in the 1993 RED, the acute toxicity of silver conducted using a silver product (Sildate) showed low acute toxicity by the oral and dermal route (Toxicity Category IV and III). No eye or skin irritation was observed with this product (Toxicity Category IV). Administration of colloidal silver in an acute oral toxicity study showed Toxicity Category II, however (USEPA, 1993). Other studies have shown varying results depending on the type of silver compound tested. For example, in one study, the oral LD_{50} in mice for colloidal silver and for silver nitrate was 100 mg/kg and 129 mg/kg, respectively. In another study in mice, 50 mg of silver nitrate caused death in 50% of dosed animals over a 14 day observation period.

In contrast to the results reported in the silver RED, contact dermatitis and allergic reactions have been reported in humans exposed to silver by the dermal route (ATSDR, 1990).

Repeated Dose (Subchronic/Chronic) Toxicity

Several older studies from the published scientific literature examined effects from repeated exposure to silver.

In a study by Day et al. (1976), random bred mice (strain not specified) were administered silver nitrate in drinking water at a concentration of 6mM (equivalent to 65 mg/kg/day). One group of 18 mice received silver nitrate for up to 12 consecutive days and were sacrificed in groups of 3 beginning on the second day of test article administration and then every 48 hours afterward until day 12. Another group of mice received silver nitrate in water for 14 weeks at the same dose. Two mice were sacrificed at 2,4,10, and 14 weeks during the study, and then 6, 9, 13, 17, and 21 weeks after the administration of silver nitrate stopped. The results of this study showed that silver granules were not visible until after 12 days drinking water exposure to silver. At this time, scattered granules were observed in the basement membrane of the glomerular loops and in the mesangium. In the group receiving silver nitrate for 14 weeks, it was reported that the basement membrane of the capillary loops became heavily labeled with silver, but Bowman's capsule and the tubular basement membrane were not significantly involved. After mice were

returned to untreated drinking water, there was no significant change in the pattern of silver distribution during the remaining 21 weeks in which the mice were studied.

In a study by Walker (1971), male Sprague-Dawley rats aged approximately 8 weeks were administered silver nitrate in drinking water at a concentration of 12 mM (130 mg/kg/day) silver nitrate. Serial sacrifice occurred singly or in pairs after 0, 2, 4, 6, 8, 10, 12, 16, 25, and 60 weeks exposure. Rats examined at 4 weeks showed silver deposits on the basement membrane detected by electron microscopy. Deposition of silver was found in two principal locations within the kidney, basement membrane and phagocytic cells. The sequence of silver deposition was reported to be glomerulus, colon, and liver after 6 weeks' exposure; choroid plexus, thyroid acinar and skin appendage basement membranes after a further 6 weeks' exposure. After 25 weeks exposure, skin surface, urinary bladder, and prostatic acinar were labeled. Rats which had been used in a separate experiment to study reversibility of silver deposition showed continued presence of silver after 4 weeks consumption of untreated water.

In a study by Olcott (1950), 131 male rats and 114 female rats (strain not specified) were administered silver nitrate in drinking water at a concentration of 63.5 mg/kg/day, apparently for the life of the animals. Controls consisted of 89 males and 99 females given untreated water. Proteinuria appeared elevated in silver treated male and female rats, but no change in creatinine was noted from urinalysis. Elevation of the weight of the left ventricle was observed in silver treated rats. The author, based upon the observations of silver deposition within the glomeruli of treated rats and thickening of the basement membrane, hypothesized that the ventricular hypertrophy occurred through the action of silver upon the kidney.

Developmental Toxicity

In a study conducted for EPA's Office of Solid Waste and Emergency Response (OSWER), Sprague-Dawley-derived (CD) rats were dosed by gavage with silver acetate in 1% aqueous methylcellulose (10, 30, or 100 mg/kg/day) or vehicle on gd 6 through 19. Silver acetate contains 64.6% silver by weight. Therefore the lowest dose (10 mg/kg/day as silver acetate) was equivalent to approximately 6.5 mg silver/kg/day. Treatment-related clinical signs were few, noted primarily in the mid and high-dose groups and consisted of weight loss, rooting after dosing, and piloerection. Maternal body weight was comparable among groups, as was maternal body weight change. A significant ($p < 0.05$) decreasing linear trend was noted for maternal body weight on gd 12, but there were no statistically significant differences between the control group and any silver acetate-treated group. Maternal body weight change corrected for gravid uterine weight, gravid uterine weight, and absolute and relative maternal liver weight were each unaffected by treatment with silver acetate. Maternal absolute feed consumption did not exhibit any dose-related trends, but was significantly decreased at the mid dose of silver acetate, but not the low or high dose, on gd 12 to 15, 15 to 18, 6 to 20, and 0 to 20. Relative maternal feed consumption (mg/kg/day) still did not exhibit any dose-related trends, and was significantly decreased at the mid dose compared to the control group only on gd 12 to 15, and 0 to 20. Similarly, but to a lesser extent, absolute maternal water consumption was decreased at the mid dose on gd 12 to 15 and 15 to 18. Relative maternal water consumption (g/kg/day) exhibited no

significant differences from the control group for any silver acetate-treated group. There were no differences among groups for the number of ovarian corpora lutea/dam, number of implantation sites/litter, or percent preimplantation loss/litter. Postimplantation/loss (resorptions, late fetal deaths, or nonlive implants/litter), liver litter size, and percent male fetuse/litter), live litter size, and percent male fetuses/litter did not differ among groups. An increasing trend was observed for the percent litters with late fetal deaths. Average fetal body weight per litter (sexes combined) and average male fetal body weight per litter exhibited a significant decreasing trend, but no significant pairwise differences between the silver acetate-treated groups and the control group. No statistically significant effects were noted for average female fetal body weight. No toxicologically relevant differences were observed in the incidences of fetal malformations or variations. The percent female fetuses with malformations per litter exhibited a significant main effect for dose (ANOVA), but no significant trend or pairwise differences between any silver acetate-treated group and the control group. A single female fetus in the low-dose group had thirteen individual types of skeletal malformations in the vertebral column, ribs, and sternum. The observation of this extensive skeletal dismorphogenesis in a single fetus from the low dose group, but not in the mid and high dose groups, suggests that the malformations were not treatment related. The maternal LOAEL for this study was considered by the authors to be 30 mg/kg/day silver acetate (19.4 mg silver/kg/day) based on clinical signs including weight loss. The maternal NOAEL was considered to be 10 mg/kg/day silver acetate (6.5 mg silver/kg/day), The NOAEL for developmental toxicity for this study was 100 mg/kg/day silver acetate (64.6 mg silver/kg/day), based on the absence of any biologically or statistically significant developmental toxicity.

Neurotoxicity

In a study by Rungby et al. (1987), two female Wistar rats were mated with the same male rat, and at birth, 2 pups were placed in the treatment group and 2 in a control group. The experimental group received daily subcutaneous injections of 0.1mg silver lactate during the first week, 0.2mg silver lactate during the second week, and 0.35 mg silver lactate during the last 2 weeks. sodium lactate was used as control. At the end of treatment, pups were euthanized and perfused with 0.5% buffered sodium sulfide perfusate. The brains were examined from 30 micron horizontal sections. The results of this study, while quite limited, demonstrated that for the pyramidal cell layer of regio superior of the hippocampus, the layer was significantly smaller in silver treated pups. Thus, the developing rat hippocampus appears to be a target of silver toxicity and requires further examination.

In a study by Rungby and Danscher (1983), 40 Wistar and Sprague-Dawley rats (male and female) were administered silver under various dosing regimens, which included: 1) silver lactate i.p. at doses ranging from 3-55 mg; 2) 0.01% silver lactate in water. Specific durations of exposure were not stated. Silver localization was performed for brain and spinal cord. Twenty-four hours following an i.p. dose of silver, the report stated that silver was observed within large motor neurons and protoplasmic astrocytes. Other sites where silver was observed to accumulate

included the hippocampus, brain stem motor nuclei, cerebellum, globus pallidus, and spinal cord. The study provides some information on the distribution of silver in the brain and spinal cord, but many experimental details are lacking to male a full evaluation.

A second study by Rungby and Danscher (1983) examined the potential of silver administered to pregnant rats to distribute into the brains of rat pups. Eight pregnant Sprague-Dawley rats received two i.p. injections of 8mg silver lactate on gestational days 18 and 19. Controls received i.p. injections of the vehicle (saline). Offspring were killed on postnatal days 1, 14, and 45, and the brains examined histopathologically for the presence of silver. Day 1 rat pups were observed with silver in the perikarya and major dendrites of large motor neurons in the developing motor nuclei of the medulla oblongata and pons and in the glia scattered throughout the brain stem. At day 14, neurons of the brain stem motor nuclei were observed with significant amounts of silver. The cerebellum was observed with silver, in contrast to day 1. In 45 day old rats, silver staining resembled that of day 14, but a larger proportion of neurons in the red nucleus and basal ganglia and the pyramidal cell layer of the hippocampus and neocortex were observed with silver. The study stated that in the rats examined, there were no obvious malformations or dysfunctions, but specific testing for neural deficits was not carried out.

Mutagenicity

In a study by Nishioka (1975), 56 metals were tested for mutagenic activity using the rec- assay. Two strains of bacillus subtilis (H17 and M45) were used for screening, and 3 strains of E. coli were used as test organisms. Results showed that for silver, there was no indication of a mutagenic effect.

In a study by Robison et al. (1982), the effect of various metal compounds on the DNA of Chinese hamster ovary cells was examined. Chinese hamster ovary cells (CHO) were seeded onto 60mm culture dishes and allowed to grow for 24 hours using radiolabeled deoxythymidine. Cells were ten allowed to grow to confluence in the absence of radiolabel. Treatment with silver sulfide at 10 μg/ml for 24 hours induced DNA strand breaks and caused reduction in molecular weight of DNA.

In a study by Rossman and Molina (1986), silver nitrate was tested up to a concentration of 0.1μM and was reported to have no significant effect on mutagenesis by UV light in E coli WP2.

Carcinogenicity

There are no recent carcinogenicity data for silver. In an older study by Furst and Schlauder (1977), intramuscular injection of silver once a month for ten months to male and female Fischer 344 rats (five doses of 5 mg silver, five doses of 10 mg silver) resulted in no increased incidence of fibrosarcomas in silver treated rats.

Metabolism and Disposition

Gregus and Klassen (1986) examined distribution and excretion of 18 metals in Sprague-Dawley rats. For silver, silver nitrate was dissolved in water and mehtylmercuric chloride, which was then dissolved in saline containing 5mM sodium carbonate. This solution of silver was administered i.v. via the saphenous vein at a dose of 0.1 mg/kg/ for urinary and fecal excretion, and at doses of 0.01, 0.03, 0.1, and 0.3 mg/kg for biliary excretion. Injections were made under ether anesthesia. After recovery, rats were placed in individual metabolic cages and urine and feces collected at 24 hour intervals for 4 days. Biliary excretion was also examined up to 2 hours after intravenous dosing. Results for silver showed a very small percentage of the dose excreted in urine (only a dose of 0.1 mg/kg was used). A total of 0.3% of the administered dose was excreted via this route. Fecal excretion was more prominent (72% of the dose after 4 days). Daily excretion was highest on the first day following injection. Biliary excretion varied with dose; 25.5% was observed at the 0.01 mg/kg dose, 44.7% at the 0.03 mg/kg dose, 32.3% at the 0.1 mg/kg dose; and 34.5% at the 0.3 mg/kg dose. Thus, the percentage excreted in bile did not vary significantly with increasing dose. Two hours after injection, tissue distribution of silver was most prominent in the liver (8.06% of the dose), kidney (1.9% of the dose), spleen (1.78% of the dose), heart (1.81% of the dose), and pancreas (2.14% of the dose).

Klassen (1979) examined biliary excretion of silver in male Sprague-Dawley rats, New Zealand White rabbits, and mongrel dogs. Doses of 0.01, 0.03, 0.1, and 0.3 mg/kg were used for rats, while a dose of 0.1 mg/kg was used for rabbits and dogs. Data reported for the rat are as described above for Gregus and Klaassen (1986). In the dog, plasma concentration of silver was markedly lower in comparison to the rat and rabbit. Excretion of silver into bile was also significantly lower in the rabbit (0.05 μg/min/kg) and dog (0.005 μg/min/kg) than in the rat (0.25 μg/min/kg). The main reason for differences in biliary excretion rate was based upon the concentration of silver in the bile and not differences in rate of bile production. Species variation was postulated to be based on differences in transfer of silver from liver to bile.

Furchner et al. (1968) examined excretion of silver in various species from various routes of administration. Radiolabeled silver as silver nitrate was administered by various routes including intraperitoneal, tail vein, or jugular sinus to mice and rats, and by oral and intravenous routes to monkeys and dogs. Doses in mice were 0.25 μCi (oral and i.p.); 0.35μCi (i.p.); 0.25μCi (tail vein); or 0.26μCi (jugular sinus). Doses in rats were 0.5μCi for all routes except i.p, where a dose of 0.4μCi was used. Doses in monkeys were 0.6μCi for both routes, and doses in dogs were 0.6μCi orally and 0.4μCi i.v.

Cumulative excretion by the intravenous route showed that fecal excretion was least in the dog (15% of administered radioactivity), followed by monkey (44%), rat (71%), and mouse (82%). By the intraperitoneal route, mice and rats were similar in fecal excretion profile (88 and 77% respectively). By the oral route, almost the whole radioactive dose was administered in feces of all species tested (90-99% excreted by this route).

2.2 Zeolite-Based Silver Compounds

In reviewing silver containing compounds, the Antimicrobials Division concluded that zeolite-based silver compounds are chemically distinct from silver salts; therefore, silver salts and silver zeolite compounds are treated separately for purposes of hazard and risk assessment (US EPA, 2004). At this time, silver salts are considered together as a group (as noted above), while hazards and risks for zeolite-based silver compounds are considered on a case-by-case basis for each silver zeolite compound at this time.

There are several end-use zeolite-based silver compound registrations that have dietary and drinking water uses. For assessment of dietary and drinking water exposure to zeolite-based silver compounds, the registrant must submit or cite valid toxicology studies in support of each zeolite-based silver compound that are required for dietary exposure assessment, including subchronic toxicity in the rodent, developmental toxicity in the rodent, and reproductive toxicity in the rodent. For a specific type of zeolite-based silver compound (e.g., silver-zinc zeolite, silver copper zeolite), toxicity data on the zeolite-based compound with the highest percentages of silver and/or silver-zinc and silver-copper should be conducted. This will support other end use formulations containing lower percentages of these metals (D287537 and D287389).

Acute Toxicity

The acute toxicity of both silver copper and silver zinc zeolite has been examined in studies submitted to the Office of Pesticide Programs. For silver copper zeolite, acute oral and dermal toxicity studies showed low toxicity (Toxicity Category IV). Acute inhalation toxicity showed Toxicity Category III. Slight dermal irritation was observed in a dermal irritation study (Toxicity Category IV). Silver copper zeolite was not a dermal sensitizer when tested in guinea pigs. Eye irritation showed moderate irritation (Toxicity Category II).

For silver zinc zeolite, the same acute toxicity categories were obtained as for silver copper zeolite except for eye irritation, where a toxicity category III was reported for silver zinc zeolite.

For silver sodium hydrogen zirconium phosphate, acute toxicity data conducted on the 10% product showed low acute oral and dermal toxicity (Toxicity Categories IV and III), minimal eye irritation (Toxicity Category III), no dermal irritation (Toxicity Category IV), and no dermal sensitization.

Subchronic Toxicity

Some subchronic toxicity data are available for silver zinc and silver copper zeolite.

For silver zinc zeolite, a 90-day oral toxicity study in dogs (MRID 45862201) was reviewed. In this study, a NOAEL of 50 mg/kg/day and LOAEL of 250 mg/kg/day were identified ,based on histopathology in the kidney in both sexes, decreased hemoglobin in males, and changes in clinical chemistry in the females.

For silver copper zeolite, a 90-day dermal toxicity study in rats was reviewed. In this study, there were no identified toxic effects up to and including a dermal dose of 1000 mg/kg/day.

For silver sodium hydrogen zirconium phosphate, a 90-day oral toxicity study in the dog was available (MRID 45345704). This study reported effects in dogs consisting of chronic granulomatous inflammation of the liver accompanied by vacuolization and necrosis observed at a dose of 1000/700 mg/kg/day.

Developmental and Reproductive Toxicity

A developmental toxicity study in rats (MRID 41638502) is available for silver zinc zeolite. In the developmental toxicity study, effects were observed only at a dose of 2000 mg/kg, above a limit dose as defined by the Agency. In a reproductive toxicity study conducted with silver zeolite A, a parental and offspring NOAEL was identified at 72/87 [M/F] mg/kg/day based on decreased body weight and food consumption, changes in hematology, cholesterol, and kidney histology in parental animals at 472/548 [M/F] mg/kg/day, and decreases in live birth index and increase in stillborn index at 472/548 [M/F] in offspring.

A 2-generation reproduction toxicity study was also available for silver sodium hydrogen zirconium phosphate (MRID 45769402). A parental systemic toxicity LOAEL was determined at a dose of approximately 2000 mg/kg/day (decreased body weights, during maturation, decreased body weights during gestation and lactation, decreased food consumption, decreased number born, and decreased live litter size). An offspring toxicity LOAEL was also determined at the 2000 mg/kg/day dose level (decreased pup and litter weights).

Mutagenicity

Available mutagenicity data for silver zinc and silver copper zeolite indicate no mutagenic activity in Ames Salmonella assays and chromosomal aberration tests for silver zinc zeolite, and in Ames Salmonella and in vivo cytogenetics for silver copper zeolite. Mutagenicity data for silver sodium hydrogen zirconium phosphate also indicate no mutagenic potential in *in vitro* studies (reverse gene mutation, micronucleus assay), but showed evidence of mutagenicity in a mouse lymphoma mammalian cell gene mutation assay, although concentrations causing this effect were close to those approaching maximum acceptable cytotoxicity.

Chronic Toxicity/Carcinogenicity

There are no acceptable data available for chronic toxicity/carcinogenicity for any zeolite-based silver compounds.

Metabolism and Disposition

There are no data available on metabolism and disposition of any of the zeolite-based silver compounds.

3. Dietary and Drinking Water Exposure

3.1 Silver/Silver salts

A dietary exposure and risk assessment will need to be conducted for silver based on the use in water filters and indirect food uses, including food handling use sites.

3.2 Zeolite-Based Silver Compounds

Zeolite-based silver compounds applications are primarily as materials preservative (Use Site Category VII) in a wide variety of applications, including applications in indirect food use exposure scenarios.

Based on the indirect food uses of zeolite-based silver compounds, a dietary and drinking water exposure and risk assessment will need to be conducted.

4. Occupational/Residential Exposure

Silver and silver salts have registrations for use in agricultural premises and equipment, food handling/storage establishments premises and equipment, commercial, institutional and industrial premises and equipment, residential and public access premises, materials preservatives, and swimming pools. These are summarized in the following table:

Table 1. Potential Use Scenarios Based on Product Labels for Silver and Silver Salts		
Use Site Category	Example Use Sites	Scenarios
Use Site Category I Agricultural Premises and Equipment	Egg products establishments, meat establishments, mushroom farms, poultry establishments, shell egg grading establishments	• Application through spraying
Use Site Categories II, III, and V Food Handling, Commercial/ Institutional/Industrial, Medical	Washable (non-food contact) surfaces: bars, cafeterias, delis, food serving areas, restaurants, school kitchens, commercial/institutional kitchens, food preparation and processing areas, food service/processing establishments	• Application to hard surfaces through coarse spraying (low pressure spray), trigger pump spray, wipe/sponge, mop, and immersion.
Use Site Category IV Residential and Public Access Premises	Hard, non –porous surfaces, vehicles/transporation, athletic facilities, spas, hot tubs, whirlpools	• Application to hard surfaces through coarse spraying (low pressure spray), trigger pump spray, wipe/sponge, mop, and immersion. Ready-to-use liquid solutions.
Use Site Category VII Materials Preservatives	Apparel; adhesives; caulks; coatings; paint; plastics; tubing; textile Finishing; water filters And water filters media	• Impregnated materials
Use Site Category XI Swimming Pools	Swimming pool algaecide	• Liquid application to pool; cartridge application in pool filter equipment

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete. For silver salts and zeolite-based silver compounds, there are potential exposures in both the occupational and residential setting.

4.1 Silver and Silver salts

For silver and silver salts, there are currently 92 registered labels. Occupational exposure would be expected from mixing/loading of manufacturing use product for incorporation into treated articles and other substrates. This exposure could involve both dermal and inhalation exposures. Residential exposures (dermal, inhalation, incidental oral) are expected from the hard surface disinfection uses for silver and the drinking water uses and swimming pool use. Infants and children as well as older individuals are also a potential subpopulation of exposure, based on residential use sites as well as registered uses in day care facilities and hospitals. Durations of exposure could involve short, intermediate, and long-term. Therefore, exposure data and/or modeling of exposure will be needed in order to adequately assess these occupational and residential exposure scenarios.

4.2 Zeolite-Based Silver Compounds

For zeolite-based silver compounds, materials preservative uses in paint, textiles, synthetic fibers would also result in occupational exposure from incorporation of the chemical into the articles intended for preservation, and residential exposure from dermal, inhalation, and incidental oral contact. Inhalation exposures may occur from use in HVAC systems.

5. Aggregate and Cumulative Exposure

In order for a pesticide registration to continue, it must be shown "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

In performing aggregate exposure and risk assessments, the Office of Pesticide Programs has published guidance outlining the necessary steps to perform such assessments (General Principles for Performing Aggregate Exposure and Risk Assessments, November 28, 2001; available at http://www.epa.gov/pesticides/trac/science/aggregate.pdf). Steps for deciding whether to perform aggregate exposure and risk assessments are listed, which include: identification of toxicological endpoints for each exposure route and duration; identification of potential exposures for each pathway (food, water, and/or residential); reconciliation of durations and pathways of exposure with durations and pathways of health effects; determination of which possible residential exposure scenarios are likely to occur together within a given time frame; determination of magnitude and duration of exposure

for all exposure combinations; determination of the appropriate technique (deterministic or probabilistic) for exposure assessment; and determination of the appropriate risk metric to estimate aggregate risk.

The Agency recognizes that in addition to the antimicrobial pesticidal uses, silver is used for a variety of nonpesticidal uses as well, which include but are not limited to: photography, cosmetics, sunscreens, manufacture of inks and dyes, mirror production, and in jewelry. These sources result in primary exposures being via the dermal route. As previously mentioned, the consequence of silver exposures via the dermal route is dermal argyria, which does not contribute to the systemic argyria induced by oral and inhalation routes of exposures.

Dermal, incidental oral, and inhalation exposures can occur from the uses of silver as an antimicrobial pesticide, and can involve short- and intermediate-term exposures. Dermal exposures would also occur from contact with treated articles. Aggregation of exposures will depend upon endpoints selected to represent effects from the various routes of exposure.

The Food Quality Protection Act (FQPA) requires that the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common toxic mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the substances individually. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for silver salts or zeolite-based silver compounds. Prior to a final Registration Review decision for silver salts and zeolite-based silver compounds, the Agency will determine if there is any new information, such as new hazard or exposure data or information on changes to the use pattern, which would affect the cumulative risk assessment. Should the Agency determine that new information on silver salts and zeolite-based silver compounds is available that could potentially impact the cumulative risk assessment and result in a risk of concern, the Agency will revisit the cumulative risk assessment. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/

Section 6. Incidents

A search of the OPP Incident Data System (IDS) found 52 silver incidents, all of which relate to Brita water filter use. Symptoms included rash, hives, severe itching, bloating and stomach problems, diarrhea, dizziness, raised blood pressure, edema, constant kidney pain, urinary tract and kidney infection, sore throat, and a dry mouth. All the effects reported are considered to be through the oral route of exposure. However, it is difficult to clearly link the incidents to the silver used in the filter.

Section 7. Anticipated Toxicology Data Needs

7.1 Silver and Silver salts

The review of the existing toxicological database for silver and silver salts showed that many of the studies cited in the RED document issued in 1993 were not sufficient for characterizing hazard and risk from exposure to silver and silver salts. However, a weight of evidence document developed within the Antimicrobials Division (Morrow, 2009) has cited current Agency regulatory levels established for silver in conducting hazard and risk assessments. These regulatory levels are based upon the effect of silver known as argyria, a permanent discoloration of the skin and/or eyes, but whast is considered to be a cosmetic and not toxicologic effect. These established regulatory levels have been used previously to assess oral and dermal risks from exposure to silver and silver salts and are considered conservative based upon the low dose levels established for protection against argyria, which is considered to be protective of systemic effects from oral and dermal exposure to silver. Therefore, studies normally requested to address indirect and/or drinking water applications of silver and silver salts will not be required. However, inhalation exposures and risks cannot be adequately assessed for silver and silver salts using this approach as there are no inhalation data for silver and silver salts, and inhalation effects have been reported in humans occupationally exposed to silver (Drake and Hazelwood, 2005).

Thus, to address inhalation exposures that can occur from silver and silver salts as is expected from uses such as the disinfectant spray uses, a 28-day inhalation toxicity study with silver aerosol wil be needed. This test can be conducted using the 870 series guideline (870.3465) for subchronic (90-day) inhalation toxicity.

7.2 Zeolite-Based Silver Compounds

To address hazard and exposure from HVAC and indirect food uses of zeolite-based silver compounds, data needs may include assessment of subchronic toxicity, developmental toxicity, inhalation toxicity, and reproductive toxicity. Specific data needs will be based on the specific zeolite-based compound and its use(s).

For example, silver sodium hydrogen zirconium phosphate has a toxicity database that is adequate for assessment of hazard based on its use pattern with the exception of a repeat dose inhalation toxicity study. The toxicity databases for silver copper and silver zinc zeolite are not as complete for assessment of risk from the registered use patterns, and specific data requirements for these zeolite compounds are listed below.
With respect to zeolite-based silver compounds, AD decided that zeolite compounds have their own toxicological pattern and zeolite-based silver-zinc active ingredients are not similar to salts of silver and zinc. Hazards would need to be considered separately for each zeolite-based silver compound. Therefore, for the purposes of registration review, toxicity data needs for the silver-zinc and zinc zeolites are as follows:

Human Health Toxicity Data Requirements for Silver copper zeolite:

- (GLN 870.3100) 90-Day Oral Toxicity-rodent
- (GLN 870.3150) 90-Day Oral Toxicity-non-rodent
- (GLN 870.3800) Reproductive Toxicity- rodent
- (GLN 870.3465) 28-Day Inhalation Toxicity-rodent

Human Health Toxicity Data Requirements for Silver zinc zeolite:

- (GLN 870.3100) 90-Day Oral Toxicity-rodent
- (GLN 870.3250) 90-Day Dermal Toxicity-rodent
- (GLN 870.3465) 28-Day Inhalation Toxicity-rodent
- (GLN 870.3700) Developmental Toxicity-rodent
- (GLN 870.3800) Reproductive Toxicity- rodent

Human Health Toxicity Data Requirements for Silver sodium hydrogen zirconium phosphate:

- (GLN 870.3465) 28-Day Inhalation Toxicity-rodent

Section 8. Anticipated Occupational and Residential Exposure Data Needs

The division anticipates data needs for assessment of occupational and residential exposure for BOTH silver/silver salts and zeolite-based silver compounds. Thus, for silver and silver salts:

- (GLN 875.1200) Dermal indoor exposure
- (GLN 875.1400) Inhalation indoor exposure
- (GLN 875.1600) Data reporting and calculations
- (GLN 875.1700) Product use information

For zeolite-based silver compounds:

- (GLN 875.1200) Dermal indoor exposure
- (GLN 875.1400) Inhalation indoor exposure
- (GLN 875.1600) Data reporting and calculations
- (GLN 875.1700) Product use information

Post-application data needs are also anticipated for silver and silver salts as well as zeolite-based silver compounds. Data will be needed for surface residues, activity patterns, and product use information. Specifically:

For silver and silver salts:

- (GLN 875.2300) Indoor surface residue dissipation
- (GLN 875.2700) Product use information
- (GLN 875.2900) Data reporting and calculations
- (GLN 875.3000) Non-dietary ingestion exposure

For zeolite-based silver compounds:

- (GLN 875.2300) Indoor surface residue dissipation
- (GLN 875.2700) Product use information
- (GLN 875.2900) Data reporting and calculations
- (GLN 875.3000) Non-dietary ingestion exposure

Section 9. Tolerances

There are currently no tolerances or exemptions for the requirement of a tolerance for any silver or silver salts in this registration review case. It is noted that the Food and Drug Administration lists silver under 21 CFR 176.300 for use as a slimicide in the manufacture of paper and paperboard that contact food, with no stated limitation.

Section 10. Overall Conclusions

The Antimicrobials Division has reviewed the hazard and exposure databases for silver/silver salts and zeolite-based silver compounds. The division anticipates that additional toxicity and exposure data will be needed for both silver/silver salts and zeolite-based silver copmpounds. For silver/silver salts, toxicology data are needed to address inhalation toxicity. For zeolite-based silver compounds, toxicology data are

needed to assess hazards from the indirect food uses. Exposure data are needed to address exposure from occupational and residential uses of silver/silver salts and zeolite-based silver compounds, and a dietary assessment and an aggregate assessment may be needed.

Section 10. References

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Appendix A
Toxicology Data Needs

1 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver /Silver salts

Study Title	Practical Utility of the Data
28-day inhalation toxicity – rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the potential effects which could occur as a result of inhalation exposures to silver such as would occur from disinfectant spray uses. The needed study will provide insight into potential adverse effects from repeated inhalation exposures. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the inhalation route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for repeated inhalation toxicity. This would provide a more complete hazard characterization of silver and silver salts in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for repeated inhalation exposures. It is possible that inhalation risk assessments could be refined using the data from this study. **4) What is triggering the need for this data?** The difficulty of predicting real world human inhalation exposure with no repeat dose inhalation toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a repeat dose (guideline) inhalation toxicity study, in order to adequately evaluate real world human exposure to silver based on how it is used (disinfectant spray uses).

2 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver copper zeolite

Study Title	Practical Utility of the Data
Rat Reproduction Study	**1) What is the value of the study?** The needed study would provide insight into concerns regarding reproduction and fertility effects of silver copper zeolite. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study may result in a change in how risks are quantified. The data would allow the Agency to conclude more definitively whether or not there are any concerns for reproductive toxicity. This would provide a more complete hazard characterization of silver copper zeolite in regards to the potential risk of reproductive toxicity. **3) How could the data affect the risk assessment?** The study may result in a change in how risks are quantified. It is possible that database uncertainties would be addressed from such a study and that additional uncertainty factors may be removed, resulting in different magnitude of the value of the endpoint used for regulation. **4) What is triggering the need for this data?** The difficulty of predicting real world human exposure with no reproductive toxicity data in the rat or other alternative information, such as SAR (structure –activity-relationship), surrogate data, and/or weight-of-evidence to the Agency triggered the need for a reproductive (guideline) toxicity study in the rat, in order to adequately evaluate real world human exposure to silver copper zeolite, particularly women in the 15-49 years of age and infants and children, based on how it is used.

870.3465	28-day inhalation toxicity – rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the potential effects which could occur as a result of inhalation exposures to silver copper zeolite such as would occur from uses in paint. The needed study will provide insight into potential adverse effects from repeated inhalation exposures. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the inhalation route for silver copper zeolite. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for repeated inhalation toxicity. This would provide a more complete hazard characterization of silver copper zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for repeated inhalation exposures. It is possible that inhalation risk assessments could be refined using the data from this study. **4) What is triggering the need for this data?** The difficulty of predicting real world human inhalation exposure with no repeat dose inhalation toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a repeat dose (guideline) inhalation toxicity study, in order to adequately evaluate human exposure to silver copper zeolite based on how it is used (paint uses).

2 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver copper zeolite

Study Title	Practical Utility of the Data
90-Day Oral Toxicity- Non-rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the repeated oral toxicity of silver copper zeolite. The needed study would provide insight into concerns regarding toxicity via the oral route in a non-rodent species. It may also provide a toxicity endpoint applicable to risk assessment **2) How would the data be used?** The study could form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for toxicity from repeated oral exposure. This would provide a more complete hazard characterization of silver copper zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. **5) What is triggering the need for this data?** The Agency has established guidance for toxicology data requirements for indirect food uses of antimicrobial pesticides which includes conduct of a 90-day oral toxicity study in the non-rodent. The use pattern for silver copper zeolite triggers the need for this study.

2 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver copper zeolite

Guideline	Study Title	Practical Utility of the Data
870.3100	Subchronic oral (90-day)– rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the repeated oral toxicity of silver copper zeolite. The needed study would provide insight into concerns regarding toxicity via the oral route. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for toxicity from repeated oral exposure. This would provide a more complete hazard characterization of silver copper zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. **4) What is triggering the need for this data?** The difficulty of predicting real world human oral exposure with no repeat dose oral toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a 90-day oral toxicity study, in order to adequately evaluate real world human exposure to silver copper zeolite from materials preservative uses, where incidental oral exposures in infants and children will occur.

3 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver zinc zeolite

Guideline	Study Title	Practical Utility of the Data
870.3465	28-day inhalation toxicity – rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the potential effects which could occur as a result of inhalation exposures to silver zinc zeolite such as would occur from uses in paint. The needed study will provide insight into potential adverse effects from repeated inhalation exposures. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the inhalation route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for repeated inhalation toxicity. This would provide a more complete hazard characterization of silver zinc zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for repeated inhalation exposures. It is possible that inhalation risk assessments could be refined using the data from this study. **4) What is triggering the need for this data?** The difficulty of predicting real world human inhalation exposure with no repeat dose inhalation toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a repeat dose (guideline) inhalation toxicity study, in order to adequately evaluate real world human exposure to silver zinc zeolite based on how it is used (paint uses).

3 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver zinc zeolite

Guideline	Study Title	Practical Utility of the Data
870.3100	Subchronic oral (90-day)– rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the repeated oral toxicity of silver zinc zeolite. The needed study would provide insight into concerns regarding toxicity via the oral route. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for toxicity from repeated oral exposure. This would provide a more complete hazard characterization of silver zinc zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. **5) What is triggering the need for this data?** The difficulty of predicting real world human oral exposure with no repeat dose oral toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a 90-day oral toxicity study, in order to adequately evaluate real world human exposure to silver zinc zeolite from materials preservative uses, where incidental oral exposures in infants and children will occur.

3 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver zinc zeolite

Guideline	Study Title	Practical Utility of the Data
870.3150	Subchronic dermal toxicity (90-day)- Rat	**1) What is the value of the study?** The Agency does not have an adequate picture of the repeated dermal toxicity of silver zinc zeolite. The needed study would provide insight into concerns regarding toxicity via the dermal route. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the dermal route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for toxicity from repeated dermal exposure. This would provide a more complete hazard characterization of silver zinc zeolite in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the oral route. **4) What is triggering the need for this data?** The difficulty of predicting real world human dermal exposure with no repeat dose dermal toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for 90-day dermal toxicity study, in order to adequately evaluate real world human exposure to silver zinc zeolite from materials preservative uses, where incidental oral exposures in infants and children will occur.

3 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver zinc zeolite

Guideline	Study Title	Practical Utility of the Data
870.3800	Rat Reproduction Study	**1) What is the value of the study?** The needed study would provide insight into concerns regarding reproduction and fertility effects of silver zinc zeolite. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study may result in a change in how risks are quantified. The data would allow the Agency to conclude more definitively whether or not there are any concerns for reproductive toxicity in the rat. This would provide a more complete hazard characterization of silver zinc zeolite in regards to the potential risk of reproductive toxicity. **3) How could the data affect the risk assessment?** The study may result in a change in how risks are quantified. It is possible that risks for silver zinc zeolite may be refined, resulting in less uncertainty around reproductive toxicity assessments. **4) What is triggering the need for this data?** The difficulty of predicting real world human exposure via oral route with no reproductive toxicity in the rat or other alternative information, such as SAR (structure –activity-relationship), surrogate data, and/or weight-of-evidence to the Agency triggered the need for a reproductive (guideline) toxicity study in the rat, in order to adequately evaluate real world human exposure to silver zinc zeolite, particularly women in the 15-49 years of age and infants and children, based on how it is used.

3 Appendix A. Toxicity Guideline Study Justifications-Case 4082-Silver zinc zeolite

Guideline	Study Title	Practical Utility of the Data
870.3700	Developmental Toxicity-Rodent	**1) What is the value of the study?** The Agency does not have adequate data to assess developmental toxicity of silver zinc zeolite. The needed study would provide data on the toxicity of silver zinc zeolite to the developing organism. It may also providea toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The data would allow the Agency to conclude more definitively whether or not there would be any concerns for developmental toxicity from exposure to silver zinc zeolite. This would provide a more complete hazard characterization of silver zinc zeolite regarding potential risks to U.S. populations and to females 13-50 years of age. **3) How could the data affect the risk assessment?** The results of the study could potentially change how risks are quantified. The hazard study could result in refined risks from oral exposures. **4) What is triggering the need for this data?** The difficulty of predicting developmental toxicity exposure with no developmental toxicity data in the rat or other alternative information, such as SAR (structure –activity-relationship), surrogate data, and/or weight-of-evidence to the Agency triggered the need for a developmental toxicity study in the rat, in order to adequately evaluate real world human exposure and developmental toxicity to silver zinc zeolite, particularly women in the 15-49 years of age and infants and children, based on how it is used.

4 Appendix A. Toxicity Guideline Study Justifications-Case 5015-Silver sodium hydrogen zirconium phosphate

Guideline	Study Title	Practical Utility of the Data
870.3465	28-day inhalation toxicity – rodent	**1) What is the value of the study?** The Agency does not have an adequate picture of the potential effects which could occur as a result of inhalation exposures to silver sodium hydrogen ziroconium phosphate such as would occur from uses in HVAC systems and paint. The needed study will provide insight into potential adverse effects from repeated inhalation exposures. It may also provide a toxicity endpoint applicable to risk assessment. **2) How would the data be used?** The study would form the foundation for hazard characterization and toxicity endpoints selection for risk assessment through the inhalation route. The data would allow the Agency to conclude more definitively whether or not there would be any concerns for repeated inhalation toxicity. This would provide a more complete hazard characterization of sodium hydrogen ziroconium phosphate in regards to the potential risks to the U.S. general population including infants and children. **3) How could the data affect the risk assessment?** The study would form the foundation for hazard characterization and toxicity endpoints selection for repeated inhalation exposures. It is possible that inhalation risk assessments could be refined using the data from this study. **4) What is triggering the need for this data?** The difficulty of predicting real world human inhalation exposure with no repeat dose inhalation toxicity data and no other alternative information, such as SAR (structure-activity-relationship), surrogate data, and/or weight-of-evidence to the Agency **triggered** the need for a repeat dose (guideline) inhalation toxicity study, in order to adequately evaluate real world human exposure to sodium hydrogen ziroconium phosphate based on how it is used (HVAC and paint uses).

Appendix B

Human Exposure Data Needs

5 Appendix B: Exposure Guideline Study Justifications: Case 4082 (silver/silver salts, silver zeolites) and Case 5015 (silver sodium hydrogen zirconium phosphate)

Guideline	Study Title	Practical Utility of the Data
875.1400 (Applicator)	Inhalation Indoor Exposure	*Note: Inhalation exposure data are needed for occupational indoor uses.* **1) What is the value of the study?** Inhalation handler exposure is expected for the open pour exposure scenario. In addition, inhalation exposures from liquid pouring are evident in exposure studies in the Pesticide Handlers Exposure Database (PHED). The significance of these exposures is directly affected by the severity of the inhalation toxicological endpoint of concern. At this point in time, no toxicological data are available to assess the inhalation risk. The existing Chemical Manufacturer Association (CMA) data base and PHED for these scenarios are limited in scope for QA/QC and the number of replicates (i.e., number of times a worker is monitored for a specific activity). EPA presented the need for additional handler exposure data to the January 2007 Science Advisory Panel (SAP) as well as to the April 2007 Human Studies Review Board (HSRB) and both groups agreed that additional data are warranted. **2) How would the data be used?** An inhalation study would be used to assess possible occupational exposures resulting from mixing/loading of manufacturing use product for incorporation into treated articles and other substrates. **3) How could the data affect the risk assessment?** The inhalation exposure data would be used to determine the accuracy of the inhalation risks to occupational workers. If risks warrant mitigation, the inhalation exposure data would allow the Agency to develop possible mitigation measures that may reduce risks of concern. Examples of mitigation may include respiratory protection using respirators, closed mixing/loading metering systems, and potential removal of uses from the label. **4) What is triggering the need for this data?**

5 Appendix B: Exposure Guideline Study Justifications: Case 4082 (silver/silver salts, silver zeolites) and Case 5015 (silver sodium hydrogen zirconium phosphate)

Guideline	Study Title	Practical Utility of the Data
		The criteria for the inhalation exposure data are based on the potential for inhalation exposure from the labeled uses and evidence of toxicity. If no toxicological endpoints of concern were identified or if potential occupational handler exposure is precluded by a closed mixing/loading requirement, then the inhalation exposure data would not be needed.
875.1200 (Applicator)	Dermal Indoor Exposure	*Note: Dermal exposure data are needed for occupational indoor uses.* **1) What is the value of the study?** The potential for dermal exposure is high for handlers that are involved in open pour exposure scenarios. The existing CMA data base and PHED data base for these scenarios are limited in scope for QA/QC and number of replicates. EPA presented the need for additional handler exposure data to the January 2007 Science Advisory Panel (SAP) as well as to the April 2007 Human Studies Review Board (HSRB) and both groups agreed that additional data are warranted. **2) How will the data be used?** The dermal exposure study would be used to assess possible occupational handler open-pour mixing/loading exposures resulting from mixing/loading of manufacturing use product for incorporation into treated articles and other substrates. **3) How could the data affect the risk assessment?** The dermal exposure data will be used to determine the accuracy of the dermal risks to occupational workers. **4) What is triggering the need for this data?** The criteria for the dermal exposure data are based on the potential for dermal exposure from the

5 Appendix B: Exposure Guideline Study Justifications: Case 4082 (silver/silver salts, silver zeolites) and Case 5015 (silver sodium hydrogen zirconium phosphate)

Guideline	Study Title	Practical Utility of the Data
		labeled uses (e.g., open pour handler exposure) and evidence of toxicity.
875.1600 (Applicator)	Data Reporting and Calculations	**1) What is the value of the study?** For all exposure studies submitted to the Agency, data reporting and calculations are needed to facilitate the review of the exposure studies submitted in support of silver/silver salts and silver zeolites. **2) How would the data be used?** The study report and all raw data/calculations would be reviewed for the adequacy of the data. **3) How could the data affect the risk assessment?** The data are needed to interpret the inhalation exposure data collected. **4) What is triggering the need for this data?** This data need is triggered if an exposure study is conducted.
875.1700 (Applicator)	Product Use Information	**1) What is the value of the study?** Product use information is a description of how the product is actually applied; it is not a field study. A description of how this product is used would provide for a comprehensive realistic assessment of its potential applications. **2) How would the data be used?** The description of the open pour methods will be used to define the exposure scenarios, which are to be assessed in the risk assessment. **3) How could the data affect the risk assessment?** A complete description of product use would ensure that the risk assessment is inclusive of the types of exposures occurring during occupational use.

5 Appendix B: Exposure Guideline Study Justifications: Case 4082 (silver/silver salts, silver zeolites) and Case 5015 (silver sodium hydrogen zirconium phosphate)

Guideline	Study Title	Practical Utility of the Data
		4) What is triggering the need for this data? The need for a risk assessment under Registration Review would require that the risk assessor understands how the product is applied.

Appendix C
Post-Application Study Needs

Appendix C- Post-application Guideline Study Justifications – Case 4082 (silver/silver salts, silver zeolites) and Case 5015 (silver sodium hydrogen zirconium phosphate).		
875.2300 (Post Application)	Indoor Surface Residue Dissipation	**1) What is the value of the study?** No data are currently available to determine the residues available for incidental oral exposure from treated textiles. As a first tier to the risk assessment 100% residue transfer is assumed. If no risk concerns are evident, this study will not be required. If risks of concern are indicated at 100% residue transfer, then this study is needed to refine the assessment. **2) How will the data be used?** Silver products are used in textiles. The measured residues from the study will be used to determine the magnitude of children's incidental oral exposure from treated textiles. **3) How could the data affect the risk assessment?** The data are needed to refine the risk estimates if risks of concern are identified assuming 100% residue transfer from treated decks. **4) What is triggering the need for this data?** The specific uses triggering the criteria for the surface residue data is the potential for incidental oral exposure from the treated textile uses. If no toxicological endpoints of concern were identified for the oral route, then the surface residue data would not be needed. Moreover, if risks of concern are not identified when 100% residue transfer is assumed, the data are not needed.
875.2900 (Post Application)	Data Reporting and Calculations	**1) What is the value of the study?** For all exposure studies this data requirement is required to facilitate the review of the data. **2) How will the data be used?** The study report and all raw data/calculations will be reviewed for the adequacy of the data. **3) How could the data affect the risk assessment?** The data are needed to interpret the residue data collected.

		4) What is triggering the need for this data? The data reporting requirement is triggered if a residue study is conducted.
875.3000 (Post Application)	Non-dietary Ingestion Exposure	**1) What is the value of the study?** The design of the non dietary ingestion exposure study can be combined with the Indoor Surface Residue Dissipation study (875.2300) to determine the available residue leaching from child mouthing treated textiles. **2) How will the data be used?** This product is used as preservative in treated textiles. The available residues from treated textiles will be used to determine the magnitude of children's incidental exposure. **3) How could the data affect the risk assessment?** The data are needed to refine the risk estimates if risks of concern are identified assuming 100% residue transfer from treated textiles. **4) What is triggering the need for this data?** The criteria for the surface residue data are the potential for incidental oral exposure. If no toxicological endpoints of concern are identified for the oral route, then the non-dietary ingestion exposure data would not be needed. Moreover, if there are no risks of concern when 100% residue transfer is assumed, the data are not needed.

Attachment 10

Chemical Properties

CAS Registry Number: 7440-22-4

Selected information from two of the National Library of Medicine's databases: ChemIDPlus[2] and HSDB[3].

Names[1]

Structure

Synonyms (Sources: **NTP**,HSDB,RTECS,MESH)[2]

- Algaedyn
- Amalgum
- Argentum
- C.I. 77820
- Germany: C-Pigment 2
- HSDB 5034
- SR 999
- Shell silver
- Silber [German]
- Silflake 135
- Silpowder 130
- Silver atom
- Silver metal
- Silver, colloidal
- TCG 7r

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Other Registry Numbers[2]

- 1022160-64-0
- 1082224-48-3
- 1187830-15-4
- 12553-68-3
- 1293966-06-9
- 1293966-27-4
- 1337956-09-8
- 172826-34-5
- 204594-09-2
- 745795-74-8
- 87354-45-8
- 87370-84-1
- 97328-41-1

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Chemical Properties[3]

Property	Description
Boiling Point	• Approx 2000 deg C
Color/Form	• Metal: White lustrous solid.

	• White metal, face-centered cubic structure
Corrosivity	• Sol silver cmpd will attack some forms of plastics, rubber, and coatings. /Silver metal and soluble silver compounds/
Critical Temperature & Pressure	• None Found
Density/Specific Gravity	• 10.49 @ 15 deg C
Dissociation Constants	• None Found
Heat Of Combustion	• None Found
Heat Of Vaporization	• None Found
Melting Point	• 960.5 deg C
Molecular Weight	• 107.86
Odor	• None Found
Other Chemical/Physical Properties	• MOLTEN METAL DISSOLVES 20 TIMES ITS VOL OF OXYGEN UNDER 1 ATM & GIVES IT UP ON SOLIDIFICATION. • Poor reflector of UV • Pure silver has highest electrical & thermal conductivity and lowest contact resistance of all metals. • Silver has the oxidation states +1, and less frequently +2; higher ones are rare. • Soft, ductile, malleable, lustrous white metal.
Relative Evaporation Rate	• None Found
Solubilities	• INSOL IN HOT OR COLD WATER, ALKALI; SOL IN NITRIC ACID; HOT SULFURIC ACID, POTASSIUM CYANIDE /Aqueous/ • Sol in fused alkali hydroxides in presence of air, fused peroxides, and alkali cyanides in presence of oxygen
Spectral Properties	• None Found
Surface Tension	• None Found
Taste	• None Found
Vapor Density	• None Found
Vapor Pressure	• None Found
Viscosity	• None Found
log P (octanol-water)	• None Found
pH	• None Found

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[3]

Uses

- BEARING LININGS IN AIR-COOLED AIRCRAFT ENGINES **PEER REVIEWED**
- Brazes and solders, coinage, jewelry, tableware, photography, photochromic glass, electrical contacts, silver thick films, electroplating, electroless plating, magnetron sputtered reflective coatings, dental amalgam, bearings in jet engines, giant magnetoresistance. **PEER REVIEWED**
- Electrical contacts; high capacity silver-zinc & silver-cadmium batteries **PEER REVIEWED**
- For Silver (USEPA/OPP Pesticide Code: 072501) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./ **PEER REVIEWED**
- For coinage, most frequently alloyed with copper or gold; for manuf tableware, mirrors, jewelry, ornaments; for electroplating; for making vessels and apparatus used in manuf medicinal chemicals, in processing foods and beverages, in handling organic acids; as catalyst in hydrogenation and oxidation processes; as ingredient of dental alloys. **PEER REVIEWED**
- MEDICATION **PEER REVIEWED**

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[2]

Notes (Sources: NTP,HSDB,RTECS,MESH)

- Silver. An element with the atomic symbol Ag, atomic number 47, and atomic weight 107.87. It is a soft metal that is used medically in surgical instruments, dental prostheses, and alloys. Long-continued use of silver salts can lead to a form of poisoning known as ARGYRIA.

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Superlist Classes [2]

- 2007 CERCLA Priority List, Rank: 214
- 2011 CERCLA Priority List, Rank: 217
- Reportable Quantity (RQ) = 1000 lb
- TWA 0.01 mg/m3 for metal and soluble compounds as Ag
- TWA 0.1 mg/m3 (metal); 0.01 mg/m3 (soluble compounds as Ag)

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Links to Additional Information [2]

- CCRIS
- ClinicalTrials.gov
- DART
- DSLD
- DailyMed
- DailyMed Mob
- DrugPortal
- EMIC
- HSDB
- HSDB Mob
- Haz-Map
- Household Products
- IRIS
- ITER
- MeSH
- MeSH Heading
- MedlinePlusAll
- MedlinePlusAll Mob
- PubChem
- PubMed
- PubMed AIDS
- PubMed Cancer
- PubMed Mob
- PubMed Toxicology
- TOXLINE
- TOXLINE Mob
- TOXMAP
- TRI2000
- TRI2001
- TRI2002

- TRI2003
- TRI2004
- TRI2005
- TRI2006
- TRI2007
- TRI2008
- TRI2009
- TRI2010
- TRI2011
- TRI2012
- TRI2013
- TRI95
- TRI96
- TRI97
- TRI98
- TRI99
- WebWISER

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Footnotes

[1] Source: the NTP's CEBS database.

[2] Source: the National Library of Medicine's ChemIDPlus , 12/28/2015.

[3] Source: the National Library of Medicine's Hazardous Substance Database , 12/28/2015.

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Toxicity Effects

CAS Registry Number: 7440-22-4

Selected toxicity information from HSDB, one of the National Library of Medicine's databases.[2] .[1]

Names

Human Toxicity Excerpts

- ... A large number of case reports of argyria, mostly resulting from the use of silver compounds in medical treatment by injection (silver arsphenamine) or by oral admin (silver nitrate) /were examined/. /It was/ concluded that the lowest total doses to produce argyria were the admin of 1 g of elemental silver by injection or 1.4 g after ingestion of small amounts each day over several months. /Silver and silver compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1398] **PEER REVIEWED**
- ... DEVELOPMENT /OF ARGYRIA (POISONING BY SILVER OR A SILVER SALT WHICH LEADS TO A PERMANENT ASHEN-GRAY DISCOLORATION OF THE SKIN, CONJUNCTIVA, AND INTERNAL ORGANS)/ FROM INHALATION THROUGH OCCUPATIONAL EXPOSURE APPEARS TO BE VERY SLOW & MAY REQUIRE YEARS.[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values, 4th ed., 1980. Cincinnati, Ohio: American Conference of Governmmental Industrial Hygienists, Inc., 1980., p. 367] **PEER REVIEWED**
- ... Formation of a meningioma was found surrounding a silver clip left from an operation two years before to remove an ependymoma in the brain of an eleven year old girl.[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-114 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- 10 cc of a 2% solution were administered intravenously (Collargol). Survival time was five minutes resulting in cyanosis, coma; death due to pulmonary edema. There was no silver found in the lung.[Hill WR, Pillsbury DM; Argyria, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-69 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- A LOCALIZED BLACKISH DISCOLORATION & /TISSUE MASS/ OF CONJUNCTIVA DEVELOPED IN PATIENT'S EYE MANY YEARS AFTER SMALL SILVER INSTRUMENT HAD BEEN ACCIDENTALLY LEFT IN TISSUES AT SITE OF OPERATION FOR STRABISMUS.[Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 910] **PEER REVIEWED**
- A St. Jude Medical Silzone was implanted in a 72-year-old female, suffering from mitral valve disease. Four months later, the patient had acute cardiac failure due to partial detachment of the prosthetic valve. The mitral annulus was ulcerated and there were multiple erosions in the myocardial tissue in contact with the prosthetic valve. Histological examination revealed chronic inflammation with hemosiderine deposits and giant cells. No allergy to silver ions was found. The silver-coated sewing cuff had caused a chronic inflammatory reaction due to a toxic reaction to silver. The Silzone valve was withdrawn from the market on January 2000.[Tozzi P et al; Eur J Cardiothorac Surg 19 (5): 729-31 (2001)] **PEER REVIEWED** PubMed Abstract
- A cross sectional study was conducted on workers engaged in manufacturing precious metal powder. Of the 27 workers, 96% had elevated urine silver concentrations and 92% had elevated blood silver concentrations. Most workers had symptoms of respiratory irritation and nose bleeds were reported in 8 workers. Deposition of silver in the cornea of the eye was detected in 5 of 8 of the long term workers. The urinary enzyme N-acetyl-B-D glucosaminidase was significantly elevated in 4 individuals and was correlated with blood silver concentrations and age.[Rosenman KD et al; Brit J Indust Med 44 (4): 267-72 (1987)] **PEER REVIEWED**
- A cross-sectional study of workers producing precious-metal powder showed a significant decr in creatinine clearance in those exposed to silver, though this may have been due to the confounding effect of cadmium. /Silver powder/[Rom, W.N. (ed.). Environmental and Occupational Medicine. 2nd ed. Boston, MA: Little, Brown and Company, 1992., p. 822] **PEER REVIEWED**
- A great many case reports of argyria associated with ingestion of silver-containing breath mints, antacids, & lozenges have been published. Chronic use of silver-containing nose drops & topical application of silver nitrate to mucous membranes have also caused argyria. Direct ocular or dermal contact with concentrated silver nitrate solutions resulted in chemical burns. /Silver and silver compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**
- A nephrotic syndrome in an obese, argyric 73 yr old man was attributed to silver deposits in the kidney. The man had used a silver containing mouthwash or gargle for 10 years (1955-1965), presumably corresponding to the absorption of a total amount of 88 g of silver. The patient showed respiratory insufficiency and a nephrotic syndrome with proteinuria, elevated alpha-2 macroglobulins, and glomerular (but not tubular) involvement. Silver deposits were found in the glomerular basement membrane.[Zech P et al; Nouv Presse Med 2: 161 (1973) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-79 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- A striking feature of argyria is the regular deposition of silver in blood vessels and connective tissue, especially around the face, conjunctiva, hands, and fingernails.[Hill WR Pillsbury DM; Argyia, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-42 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Case reports were cited for four radiographers who were placed in danger due to the x-ray processing chemical fumes present in their workspace. These four cases encompass nearly all the 19 symptoms which have been associated with reactions to chemical fumes: severe headaches, sore throat/hoarseness, nasal discharge, sore eyes, unexpected fatigue, sinus problems, nausea, painful joints, bad taste in mouth, mouth ulcers, catarrh, tinnitus, tight chest, skin rash, lip sores, shortness of breath, unusual heart rhythms, chest pains, and numb extremities. Three of the four workers eventually had to give up work in radiography, and continued to experience sensitivity to radiographic chemicals and other substances such as automotive exhausts, cigarette smoke, paint fumes and red wine. The fourth radiographer was engaged in silver recovery starting in 1958; he suffered upper respiratory symptoms and recurring bouts of unexplained pneumonia starting in 1970 until 1983 when he started to use a full face mask and canister during silver recovery.[Gordon M; Radiography 53 (608): 85-9 (1987)] **PEER REVIEWED** PubMed Abstract
- Collargol was used /iv/ to fill the renal pelvis for X-ray study and resulted in severe hemorrhagic diathesis with parenchymatous hemorrhages in the stomach, intestines, and body cavities ending in death. /Argyrol/[Hill WR, Pillsbury DM; Argyria, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-69 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- High local concn of silver from a prosthetic cement were associated with a slowly resolving focal neuropathy.[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1060] **PEER REVIEWED**
- IN INDUSTRY ARGYRIA FOLLOWING EXPOSURE TO SILVER MAY BE LOCALIZED OR GENERALIZED. LOCALIZED FORM OCCURS CHIEFLY DURING HANDLING OF METALLIC SILVER, WHEN PARTICLES BECOME IMBEDDED IN SKIN & SC TISSUES, EYE LESIONS MAY ALSO BE

MANIFESTATION. ...[Browning, E. Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 298] **PEER REVIEWED**

- In one case report of a worker who had become ill 14 hr after he had been working with molten silver ingots, symptoms were limited primarily to the respiratory system ... . Unfortunately, the concn and chemical comp of the silver in the work room air were not known, and the history of exposure to silver prior to this incident was not reported. The initial symptoms seen in this patient incl audible crackles during breathing, rapid pulse, low oxygen content of capillary blood, and scattered thickening of the lungs observed in chest radiograms. The patient's symptoms progressed to acute respiratory failure, from which the patient eventually recovered fully. /Silver/[DHHS/ATSDR; Toxicological Profile for Silver p. 13 TP-90-24 (1990)] **PEER REVIEWED**
- It has been postulated that nickel/cobalt and nickel/palladium exhibit coreactivity in patients allergic to metals. OBJECTIVES: (1) Determine the incidence rate and the source for the induction of metal allergy in 3 groups of men: unpierced, one site pierced, and multiple sites pierced; and (2) evaluate the degree of coreactivity between nickel/cobalt and nickel /palladium. ... The source of the induction of the allergic accounted for 5 of 6 nickel allergies and 2 of 3 gold allergies. Silver jewelry was a significant predictor of an allergic response.[Enrlich A et al; Am J Contact Dermat 12 (3): 151-5 (2001)] **PEER REVIEWED** PubMed Abstract
- METALLIC SILVER MAY BE INHALED BY SILVER FINISHERS LEADING TO ABNORMAL CHEST X-RAY FINDINGS. ... ITS IMPORTANCE LIES IN FAILURE TO RECOGNIZE CAUSE OF SUCH X-RAY CHANGES RESULTING IN UNNECESSARY DIAGNOSTIC STUDIES OR EXCLUSION FROM EMPLOYMENT.[Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974., p. 171] **PEER REVIEWED**
- OBJECTIVE: Discoloration of the oral mucosa due to amalgam may appear histologically merely as brown pigmentation of the fibrous extracellular matrix. It was the aim of these investigations to identify the fibrous component that contains silver granules. METHODS: Biopsy specimens from seven patients with clinically diagnosed amalgam tattoos were investigated by light and electron microscopy as well as by X-ray microanalysis. RESULTS: Light microscopy revealed small brown discolored fibers in all specimens; in sections stained with Weigert's resorcinfuchsin, they appeared dark violet. Scanning electron microscopy revealed metallic granules associated with thin fibers; by X-ray microanalysis, they exhibited preferentially peaks for silver and sulfur. Transmission electron microscopy detected only electron-dense particles in elastic fibers. CONCLUSIONS: With the different morphological methods, silver granules of amalgam tattoos were exclusively detected within elastic fibers. This result indicates that granular brown discoloration of the matrix fibrils is due to silver impregnation of elastic fibers. Therefore, the histopathological diagnosis of amalgam tattoo is possible even in the absence of larger amalgam particles with black appearance.[Mohr W, Gorz E et al; HNO 49 (6): 454-7 (2001)] **PEER REVIEWED** PubMed Abstract
- Potential symptoms as a result of exposure /to silver, metal, and sol cmpd (as Ag)/: Blue-gray eye, nasal septum, throat, skin; irritation skin, ulceration; GI. /Silver, metal, and sol cmpd (as Ag)/[NIOSH. Pocket Guide to Chemical Hazards. 5th Printing/Revision. DHHS (NIOSH) Publ. No. 85-114. Washington, D.C.: U.S. Dept. of Health and Human Services, NIOSH/Supt. of Documents, GPO, Sept. 1985., p. 209] **PEER REVIEWED**
- Silver concentrations in human tissues apparently increase with age. It has been detected in fetal livers and placentae.[Robkin MA et al; Trans Am Nucl Soc 17: 97 (1973) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-1 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Silver in metallic form is harmless with the possible exception of colloidal silver preparations.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 922] **PEER REVIEWED**
- Silver may be a cause of metal fume fever.[Haddad, L.M. and Winchester, J.F. Clinical Management of Poisoning and Drug Overdosage. Philadelphia, PA: W.B. Saunders Co., 1983., p. 662] **PEER REVIEWED**
- Silver metal and soluble silver compounds can cause discoloration or blue-grey darkening of the eyes, nose, throat, and skin. /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1] **PEER REVIEWED**
- The organs which are affected by exposure to silver, metal, and sol cmpd (as Ag) are nasal septum, skin, eyes. /Silver, metal, and sol cmpd (as Ag)/[NIOSH. Pocket Guide to Chemical Hazards. 5th Printing/Revision. DHHS (NIOSH) Publ. No. 85-114. Washington, D.C.: U.S. Dept. of Health and Human Services, NIOSH/Supt. of Documents, GPO, Sept. 1985., p. 209] **PEER REVIEWED**
- The staining of skin by silver is termed argyria and is grey-blue in colour. This may be caused by a number of mechanisms such as ingestion and direct implantation. We report an unusual case, caused by an impacted earring, where the skin discoloration was not entirely typical of argyria. This may have been due to copper impurities present in the earring.[Sugden P et al; Br J Plast Surg 54 (3): 252-3 (2001)] **PEER REVIEWED** PubMed Abstract
- There is no evidence that silver or its compounds are carcinogenic to man.[Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 1888] **PEER REVIEWED**

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Non-Human Toxicity Excerpts

- A simple, rapid assay, based on the lysosomal incorporation of neutral red by cells, conveniently carried out in 96 well microtiter plates, was used to evaluate the cytotoxic effect of cationic and anionic metal salts on BALB/c mouse 3T3 fibroblasts. Ranking of the metals according to their decreasing potency was based on spectrophotometrically determined absorbance of the neutral red, extracted from surviving viable cells. The rank order was cadmium > mercury > silver > zinc > manganese > copper > cobalt > nickel > chromium (III) for the cationic metals. Cationic metals incubated with cultures in medium containing 1% fetal bovine serum were 3-4 times more toxic than in medium with 10% fetal bovine serum.[Borenfreud E, Puerner JA; Toxicol 39 (2): 121-34 (1986)] **PEER REVIEWED**
- Adult crayfish (Cambarus diogenes diogenes) exposed to 8.41 +/- 0.17 microg silver/L (19.4% as Ag+) in moderately hard freshwater under flow-through conditions for 96 h exhibited ionoregulatory disturbance, elevated metabolic ammonia (T(amm)) production and substantial silver accumulation in the gills, hemolymph, and hepatopancreas. The ionoregulatory disturbance included both a generally reduced unidirectional Na+ influx and an increased unidirectional Na+ efflux, leading to a substantial net loss of Na+ from the silver-exposed crayfish. The Na+ uptake in silver-exposed crayfish differed overall from controls, while the increased Na+ efflux recovered to control values 48 hr into the 96 h of exposure. The general inhibition of Na+ uptake could be explained by a reduced sodium/potassium-adenosine triphosphatase (Na/K-ATPase) activity in terminally obtained gill samples from the silver-exposed crayfish. The silver-induced effect on Na+ uptake and loss translated to reduced hemolymph Na+ concentrations but not significantly reduced hemolymph Cl- concentrations. Hemolymph T(anim) and T(amm) efflux both increased in silver-exposed crayfish, indicating an increased metabolic T(amm) production. The present study demonstrates that the toxic mechanism of waterborne silver exposure in freshwater crayfish resembles that of freshwater teleost fish. The crayfish might therefore be a useful model system for extending current environmental regulatory strategies, currently based on teleost fish, to invertebrates.[Grosell M et al; Environ Toxicol Chem 21 (2): 369-74 (2002)] **PEER REVIEWED** PubMed Abstract
- Exposure of Nostoc muscorum to different concentrations of nickel and silver brought about reduction in growth, carbon fixation, heterocyst production, and nitrogenase activity and increase in the loss of ions (K+, Na+). In an attempt to ameliorate the toxicity of test metals by ascorbic acid, glutathione, and sulfur containing amino acids (L-cysteine and L-methionine), it was found that the level of protection by ascorbic acid and glutathione was more for Ag than nickel. However, metal induced inhibition of growth and carbon fixation was equally ameliorated by methionine. But the level of protection by cysteine was quite different, ie, 27% for nickel and 22% for Ag.[Rai LC, Raizada M; Ecotox Environ Safety 14 (1): 12-21 (1987)] **PEER REVIEWED**
- In a carcinogenicity study in rats, colloidal silver (dose unspecified) injected subcutaneously resulted in tumors in 8 of 26 rats surviving more than 14

months. In 6/8 rats, the tumor was at the subcutaneous injection site. In 700 untreated rats, the rate of spontaneous tumor formation was 1 to 3%; no vehicle control was reported ... .[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.10 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

- In a rat carcinogenicity study designed to avoid solid state carcinogenesis, a suspension of silver powder in trioctanion was given once a month by intramuscular (i.m.) injection to Fischer 344 rats (50/sex/group). The dose given was 5 mg each for 5 treatments and 10 mg each for 5 more treatments, for a total of 75 mg of silver. ... No fibrosarcomas (0/50) appeared at the injection site in silver treated animals. Injection site sarcoma were found only in the vehicle control (1/50) ... . The latent period in the vehicle control group was 19 months, ... The authors concluded that finely divided silver powder injected i.m. did not induce cancer ... .[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.10 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**
- Macrophages were obtained by washing the peritoneum of four unstimulated adult male NMRI-mice with isotonic buffered saline. Upon settling of cells, four cultures derived from each mouse were exposed to 80 or 20 micromolar silver lactate, 80 micromolar sodium lactate, or control medium. Macrophages exposed to either concentration of silver lactate exhibited reduced survival as compared to controls. Cells exposed to the highest silver concentration granulated and fragmented while still attached to the culture substrate. Cells exposed to the lower silver concentration released from the substrate. Silver grains were observed by microscopy in all silver treated cells, invariably located in lysosome like dense bodies. In addition, significant enhancement of malondialdehyde production was observed in liver tissue derived from mice administered silver lactate by the intraperitoneal route. No significant difference in hepatic malondialdehyde production was observed in animals treated for 3 days or with a single silver lactate injection.[Rungby J et al; Arch Toxicol 59 (6): 408-12 (1987)] **PEER REVIEWED** PubMed Abstract
- Percutaneous silver wire implants were looped through the dorsal skin of rats and inoculated with Staphylococcus aureus to test the effect on bacteria in the tract. ... No giant cells or toxicity were seen.[Spadaro JA et al; J Biomed Matter Res 20 (5): 565-77 (1986)] **PEER REVIEWED**
- Repeated exposure of animals to silver may produce anemia, cardiac enlargement, growth retardation, and degenerative changes in the liver.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 622] **PEER REVIEWED**
- SILVER FOIL WAS FOUND TO BE HIGHLY TOXIC WHEN IMPLANTED IN BRAIN TISSUES OF ANIMALS WHILE SC IMPLANTATION OF THIN SILVER FOIL INDUCES FIBROSARCOMAS IN RATS.[Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 36] **PEER REVIEWED**
- Silver metal in the rabbit anterior chamber causes little reaction, and in the vitreous body induces no clinically evident inflammation, but atrophic changes in the retina have been found by microscopic exam. In the cornea, silver particles become ensheathed in a connective tissue coating, and the surface is discolored by gray-white material assumed to be silver chloride, and also by black material assumed to be silver sulfide.[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 817] **PEER REVIEWED**
- Silver metal in the rabbit eye anterior chamber causes little reaction, and in the vitreous body induces no clinically evident inflammation, but atrophic changes in the retina have been found by microscopic exam. In the cornea, silver particles become ensheathed in a connective tissue coating, and the surface is discolored by gray-white material assumed to be silver chloride, and also by black material assumed to be silver sulfide.[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 817] **PEER REVIEWED**
- Silver, either as silver metal or silver chloride, exerted toxic effects on the smooth muscle of isolated cannulated hamster cheek pouch arterioles. Silver initially stimulated the smooth muscle, producing a marked vasoconstriction. The vessels then dilated back to control diameters. Once the arterioles began to dilate, they became refractory to norepinephrine or potassium stimulation.[Jackson Wf, Duling BR; Circ Res 53 (1): 105-8 (1983)] **PEER REVIEWED** PubMed Abstract
- The ultrastructural localization of silver deposits was noted in the eye of rats exposed to silver either perorally or intraperitoneally. Silver was found in lysosomes of most cell types, an exception being the neural retina. Extracellularly, silver was present in vascular basal laminae an in connection with connective tissue fibers. Systemic silver intoxication was found to result in a rapid and long lasting deposition of the metal in the eye.[Rungby J; Exp Mol Pathol 45 (1): 22-30 (1986)] **PEER REVIEWED** PubMed Abstract

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Human Toxicity Values

- None found

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Non-Human Toxicity Values

- LD50 Rat (male) dermal > 2000 mg/kg[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**
- LD50 Rat (male) oral >5000 mg/kg[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

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Absorption, Distribution And Excretion

- ... /An/ elimination pattern was detected in rats after iv administration of silver ... . Most of the radioactivity found in the feces was eliminated via the bile ... .[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**
- ... determined that biliary excretion accounted for between 24% and 45% of the silver admin to rats. The concn of silver in the bile was est to be between 16 and 20 times greater than that in plasma. An incr in the bile/liver tissue ratio (ug/ml per ug/g) from 4.2 to 6.4 indicates that more silver is concentrated in the bile as the dose of silver incr. It is believed that active transport is involved in the transfer of silver from the plasma to the bile ... . [DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**
- ... reported that 96.9%, 2.4%, and 0.35% of the dose /of metallic silver/ initially deposited in the lungs of a dog following intratracheal admin was detected in the lungs, liver and blood, respectively, 6 hr after exposure. The remaining silver was detected in the gall bladder and bile (0.14%), intestines (0.10%), kidneys (0.06%), and stomach (0.02%). The distribution of metallic silver (expressed as a percentage of the initial amt deposited) 225 days after exposure differed from that at 6 hr, with the majority of the metal detected in the liver (0.49%), brain (0.035%), gall bladder and bile (0.034%), intestines (0.028%), lungs and trachea (0.019%), bone (0.014%), stomach and contents (0.012%), heart (0.009%), and muscle (0.007%). The distribution to tissues other than the lungs is similar at 6 hr and 225 days if silver in the lungs is not considered. At both time points the majority of the silver is found in the liver (approx 77% of the total body silver excluding lung content).[DHHS/ATSDR; Toxicological Profile for Silver p. 27 TP-90-24 (1990)] **PEER REVIEWED**

- A study in dogs indicates that absorption of inhaled metallic silver particles with a median aerodynamic diameter of approximately 0.5 um is extensive, and is not dependent upon particle size ... . Absorption was measured in one dog that remained anesthetized during the entire period between exposure and sacrifice. In this dog, 3.1% (0.8 ug) of the deposited material was dissolved, transported out of the lungs, and was found mostly in liver and blood 6 hr after exposure; a 1 ug/cm2/day absorption rate for metallic silver was est by the authors. Up to 90% of the deposited silver was est to be absorbed into the systemic circulation based on all experimental data.[DHHS/ATSDR; Toxicological Profile for Silver p. 24 TP-90-24 (1990)] **PEER REVIEWED**
- Absorption upon exposure or the extent of exposure, itself, may vary considerably among normals as reflected in tissue levels. For example, the silver content of the hair of school children from 21 school districts in Selesia, Poland, ranged from 0.23 to 1.96 mg/kg (average 0.69 mg/kg; analyses by neutron activation).[Dutkuwicz T et al; Chem Anal 23: 261 (1978) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-1 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Distribution of silver in the rat at day 6 following intramuscular injections of 1.0 mg dose of silver; 53.5 percent of the dose was absorbed (0.59 percent absorbed by the heart and lung; 2.69 percent absorbed by spleen; 3.03 percent absorbed by blood; 33.73 percent absorbed by liver; 0.63 percent absorbed by kidney; 8.21 percent absorbed by GI tract; 2.39 percent absorbed by muscle; 2.20 percent absorbed by bone; 7.39 percent absorbed by skin; 1.82 percent excreted by urine; 37.33 percent absorbed by feces) and 46.5 percent of absorbed by the heart and lung; 0.01 percent absorbed by spleen; 0.50 percent absorbed by blood; 0.36 percent absorbed by liver; 0.07 percent absorbed by kidney; 1.12 percent absorbed by GI tract; 0.27 percent absorbed by muscle; 0.18 percent absorbed by bone; 0.24 percent absorbed by skin; 0.64 percent excreted by urine; 96.56 percent excreted in feces) and 7.9 percent was unabsorbed.[Scott KG, Hamilton JG; J Clin Invest 27: 555 (1948) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-47 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Excretion of silver from the body is mainly gastrointestinal. Urinary excretion (around 10 ug/day) and fecal elimination (30-80 ug/day) has been reported from two healthy subjects. ... These values might reflect a certain overestimation of true silver concn. ... Using neutron activation analysis ... 1 ug/day /was found/ in urine of normal persons.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 621] **PEER REVIEWED**
- Fecal elimination by rats, dogs, & monkeys accounts for up to 99% of the ingested silver. /Silver and compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**
- IF DUST OF METAL OR ITS SALTS IS ABSORBED, IT IS PRECIPITATED IN TISSUES IN METALLIC STATE & CANNOT BE ELIMINATED FROM BODY IN THIS STATE. /SILVER & CMPD/[International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983., p. 2047] **PEER REVIEWED**
- In dogs, lung clearance of metallic silver particles (avg aerodynamic diameter of 0.5 um) following intra-tracheal intubation was accompanied by an incr in silver conc in the area of the stomach and liver. The incr in silver concn in the stomach suggests that some proportion of the silver particles are cleared by the mucociliary escalator and swallowed. However, the predominant route of clearance from the lung appeared to be through dissolution of the silver and transport through the blood. The silver was apparently carried by the blood to the liver, with little cleared via the mucociliary passages ... . Approx 90% of the inhaled dose was excreted in the feces within 30 days of exposure.[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-90-24 (1990)] **PEER REVIEWED**
- In rats, silver was unevenly distributed in organs and tissues following iv or im injection of radiolabeled metallic silver and/or silver nitrate, respectively. The highest concn were found, in decr order, in the GI tract, liver, blood, kidney, muscle, bone, and skin following im injection ... . Following iv injection the highest concn were found, in decr order, in the liver, pancreas, spleen, and plasma ... . the proportion of the dose distributed to the tissues is positively correlated with the dose admin ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 28 TP-90-24 (1990)] **PEER REVIEWED**
- Rats excreted silver in the bile at 10 times the rate of rabbits. Dogs excreted silver in the bile at a rate lower than that of rabbits ... . Dogs had the highest amt of silver retained in the liver (2.9 ug silver/g), as compared to the rabbit (2.13 ug silver/g) and rat (1.24 ug silver/g).[DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**
- Regardless of route and chemical form administered, fecal excretions of silver always predominate over urinary excretion. Most absorbed silver is excreted into the intestine by the liver via the bile. /Silver/[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-56 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Silver is absorbed after topical application, ingestion, or inhalation. GI uptake ranges from <1% of the admin dose in rats, mice, & monkeys to as much as 10% in dogs. Following intratracheal admin of 0.5 um metallic silver particles, 97% of the dose remained in dog lung at 6 hr after treatment; the rate of systemic absorption was calculated as 1 ug/sq cm/day. Of the absorbed silver, 77% of the dose was found in dog liver at 225 days after admin. Pulmonary clearance was triphasic with half-times of 1.7, 8.4, & 40 days. Parenteral injection of metallic silver or silver nitrate demonstrated that rat, dog, & rabbit liver & gut retained the highest silver concns. Silver was eliminated primarily in the bile. /Silver and compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**
- Silver removal from the liver by biliary excretion was demonstrated ... . Control rats and rats with ligated bile ducts were admin radioactive metallic silver by im injection. In rats with ligated bile ducts, excretion of silver in the feces was 19%, compared to 97% in controls. Deposition in the liver of rats with ligated bile ducts was 48% and 2.5% in the GI tract compared to 0.36 and 1.12%, respectively in the controls ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**
- Silver was found only as a lipoid-silver complex or in lipofuschin-like lysosomes & in residual bodies. The lysosomes were thought to be responsible for the intracellular transport & extrusion of silver. In the liver, there was incr activity of cytochrome oxidase, but marked decr in the activity of succinate dehydrogenase. /Silver/[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-49 (1980) EPA 440/5-80-071] **PEER REVIEWED**
- Silver, once deposited in the body, is poorly excreted in the urine in amounts detectable by spectrochemical methods. /Silver metal and soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**
- Takenaka S et al; Environ Health Perspect 109 Suppl 4: 547-51 (2001)] The cardiovascular system is currently considered a target for particulate matter, especially for ultrafine particles. In addition to autonomic or cytokine mediated effects, the direct interaction of inhaled materials with the target tissue must be examined to understand the underlying mechanisms. In the first approach, pulmonary and systemic distribution of inhaled ultrafine elemental silver (EAg) particles was investigated on the basis of morphology and inductively coupled plasma mass spectrometry (ICP-MS) analysis. Rats were exposed for 6 hr at a concentration of 133 microg EAg m(3) (3 x 10(6) cm(3), 15 nm modal diameter) and were sacrificed on days 0, 1, 4, and 7. ICP-MS analysis showed that 1.7 microg Ag was found in the lungs immediately after the end of exposure. Amounts of Ag in the lungs decreased rapidly with time, and by day 7 only 4% of the initial burden remained. In the blood, significant amounts of Ag were detected on day 0 and thereafter decreased rapidly. In the liver, kidney, spleen, brain, and heart, low concentrations of Ag were observed. Nasal cavities, especially the posterior portion, and lung-associated lymph nodes showed relatively high concentrations of Ag. For comparison, rats received by intratracheal instillation either 150 microL aqueous solution of 7 microg silver nitrate (AgNO(3) (4.4 microg Ag) or 150 microL aqueous suspension of 50 microg agglomerated ultrafine EAg particles. A portion of the agglomerates remained undissolved in the alveolar macrophages and in the septum for at least 7 days. In contrast, rapid clearance of instilled water-soluble AgNO(3) from the lung was observed. These findings show that although instilled agglomerates of ultrafine EAg particles were retained in the lung, Ag was rapidly cleared from the lung after inhalation of ultrafine EAg particles, as well as after instillation of AgNO(3), and entered systemic pathways. **PEER REVIEWED**
- The clearance of radioactive silver metal dust in a man who was accidentally exposed illustrated the rapid removal of silver from the lungs primarily by

ciliary action, with subsequent ingestion and ultimate elimination in the feces ... . Lung clearance fit a biexponential profile ... . Radioactive silver was detected in the feces up to 300 days after exposure, but was not detected in urine samples (collected up to 54 days after exposure).[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-90-24 (1990)] **PEER REVIEWED**

- The deposition fraction of 0.5 um spherical silver particles in the lung of dogs has been found to be about 17%. ... The intestinal absorption of silver by mice, rats, monkeys, and dogs has been recorded at about 10% or less following ingestion of radioactive silver.[Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 524] **PEER REVIEWED**
- The deposition fraction of 0.5 um spherical silver-particles in the lung of dogs has been found to be about 17%. ... The intestinal absorption of silver by mice, rats, monkeys, & dogs has been recorded at about 10% or less following ingestion of radioactive silver. /Silver/[Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 524] **PEER REVIEWED**
- Using whole-body spectrometer measurements obtained from a person accidently exposed to radiolabeled silver, ... estimated that 25% of the detectable (110 m)Ag was distributed to the liver between 2 and 6 days after exposure.[DHHS/ATSDR; Toxicological Profile for Silver p. 27 TP-90-24 (1990)] **PEER REVIEWED**

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Metabolism/Metabolites

- None found

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Tsca Test Submissions

- None found

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Footnotes

[1] Source: the NTP's CEBS database.

[2] Source: the National Library of Medicine's Hazardous Substance Database , 12/28/2015.

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Attachment 11

Registry of Toxic Effects of Chemical Substances (RTECS)

Silver

RTECS

VW3500000

CAS

7440-22-4

Updated

September 201

Molecular Weight

107.87

Molecular Formula

Ag

Synonyms

Argentum
C.I. 77820
L-3
Shell silver
Silber (German)
Silver (ACGIH:OSHA)
Silver atom

Tumorigenic Data and References

Route/Organism	Dose	Effect	Reference
implant/mouse	lowest published toxic dose: 11 gm/kg	Tumorigenic: Equivocal tumorigenic agent by RTECS criteria	NATWAY (reference.html#NATWAY) 42,75,1955

		Tumorigenic: Tumors at site of application	
implant/rat	toxic dose: 2570 mg/kg	Tumorigenic: Equivocal tumorigenic agent by RTECS criteria Tumorigenic: Tumors at site of application	NATWAY (reference.html#NATWAY) 42,75,1955
implant/rat	lowest published toxic dose: 2400 mg/kg	Tumorigenic: Equivocal tumorigenic agent by RTECS criteria Tumorigenic: Tumors at site of application	CNREA8 (reference.html#CNREA8) 16,439,1956
multiple/rat	lowest published toxic dose: 330 mg/kg/43W-intermittent	Tumorigenic: Equivocal tumorigenic agent by RTECS criteria Tumorigenic: Tumors at site of application	ZEKBAI (reference.html#ZEKBAI) 63,586,1960

Acute Toxicity Data and References

Route/Organism	Dose	Effect	Reference
oral/guinea pig	Lethal dose: >5 gm/kg		GTPZAB (reference.html#GTPZAB) 27(12),33,1983
oral/mouse	lethal dose (50 percent kill): 100 mg/kg		ENTOX* (reference.html#ENTOX*) ,17,2005
oral/mouse	Lethal dose: >10 gm/kg		GTPZAB (reference.html#GTPZAB) 27(12),33,1983

Other Multiple Dose Data and References

Route/Organism	Dose	Effect	Reference
oral/rat	lowest published toxic dose: 8400 mg/kg/28D-intermittent	Blood: Changes in serum composition (e.g. TP, bilirubin, cholesterol) Blood: Changes in erythrocyte (RBC) count Biochemical: Enzyme	TOXID9 (reference.html#TOXID9) -,90,2008

		inhibition, induction, or change in blood or tissue levels: Phosphatases	
oral/rat	lowest published toxic dose: 8400 mg/kg/28D-intermittent	Liver: Other changes Blood: Changes in serum composition (e.g. TP, bilirubin, cholesterol) Biochemical: Enzyme inhibition, induction, or change in blood or tissue levels: Phosphatases	TOXID9 (reference.html#TOXID9) -,90,2008

Reviews

Organization	Standard	Reference
American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold Limit Value-time-weighted average 0.1 mg/m^3	DTLVS* (reference.html#DTLVS*) TLV/BEI,2013
TOXICOLOGY REVIEW		FOREAE (reference.html#FOREAE) 7,313,1942
TOXICOLOGY REVIEW		MIBUBI (reference.html#MIBUBI) 9,321,1975
TOXICOLOGY REVIEW		PTPAD4 (reference.html#PTPAD4) 1,127,1976
TOXICOLOGY REVIEW		AJMEAZ (reference.html#AJMEAZ) 38,409,1965
TOXICOLOGY REVIEW		PEXTAR (reference.html#PEXTAR) 12,102,1969
TOXICOLOGY REVIEW		CRTXB2 (reference.html#CRTXB2) 37,237,2007
TOXICOLOGY REVIEW		ENTOX* (reference.html#ENTOX*) -,17,2005
TOXICOLOGY REVIEW		TOPADD

		(reference.html#TOPADD) 32(Suppl. 2),71,2004
TOXICOLOGY REVIEW		HBTME* (reference.html#HBTME*) ,809,2007
TOXICOLOGY REVIEW		HUTOX* (reference.html#HUTOX*) -,515,1996

Standards and Regulations

Organization	Standard	Reference
Environmental Protection Agency (EPA) Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 1988 PESTICIDE SUBJECT TO REGISTRATION OR RE-REGISTRATION		FEREAC (reference.html#FEREAC) 54,7740,1989
Environmental Protection Agency (EPA) Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 1998 STATUS OF PESTICIDES	RED Completed	RBREV* (reference.html#RBREV*) -,335,1998
Mine Safety and Health Administration (MSHA) STANDARD-air	time-weighted average 0.01 mg/m^3	DTLVS* (reference.html#DTLVS*) 3,231,1971
Occupational Exposure Limit IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN check ACGIH TLV;		(reference.html#)
Occupational Exposure Limit IN SINGAPORE, VIETNAM check ACGIH TLV		(reference.html#)
Occupational Exposure Limit-AUSTRALIA	time-weighted average 0.1 mg/m^3, JUL2008	(reference.html#)
Occupational Exposure Limit-AUSTRIA	MAK-TMW 0.1 mg/m^3;KZW 0.1 mg/m^3, inhal, 2007	(reference.html#)
Occupational Exposure Limit-BELGIUM	time-weighted average 0.1 mg/m^3, MAR2002	(reference.html#)
Occupational Exposure Limit-DENMARK	time-weighted average 0.01 mg/m^3 (dust), MAY2011	(reference.html#)
Occupational Exposure Limit-EC	time-weighted average 0.1 mg/m^3, JUN2000	(reference.html#)
Occupational Exposure Limit-FINLAND	time-weighted average 0.1 mg/m^3, NOV2011	(reference.html#)

	0.1 mg/m³, NOV2011	
Occupational Exposure Limit-FRANCE	VME 0.1 mg/m³, FEB2006	(reference.html#)
Occupational Exposure Limit-GERMANY	MAK 0.1 mg/m³, inhal, 2011	(reference.html#)
Occupational Exposure Limit-HUNGARY	time-weighted average 0.1 mg/m³, short term exposure limit 0.4 mg/m³, SEP2000	(reference.html#)
Occupational Exposure Limit-ICELAND	time-weighted average 0.01 mg/m³, dust, NOV2011	(reference.html#)
Occupational Exposure Limit-JAPAN	Occupational Exposure Limit 0.01 mg/m³, MAY2012	(reference.html#)
Occupational Exposure Limit-KOREA	time-weighted average 0.1 mg/m³, 2006	(reference.html#)
Occupational Exposure Limit-MEXICO	time-weighted average 0.1 mg/m³, 2004	(reference.html#)
Occupational Exposure Limit-NEW ZEALAND	time-weighted average 0.1 mg/m³, JAN2002	(reference.html#)
Occupational Exposure Limit-NORWAY	time-weighted average 0.01 mg/m³, JAN1999	(reference.html#)
Occupational Exposure Limit-PERU	time-weighted average 0,1 mg/m³, JUL2005	(reference.html#)
Occupational Exposure Limit-RUSSIA	short term exposure limit 1 mg/m³, JUN2003	(reference.html#)
Occupational Exposure Limit-SWEDEN	time-weighted average 0.1 mg/m³, JUN2005	(reference.html#)
Occupational Exposure Limit-SWITZERLAND	MAK-week 0.1 mg/m³, KZG-week 0.8 mg/m³, inhal, JAN2011	(reference.html#)
Occupational Exposure Limit-THE NETHERLANDS	MAC-TGG 0.1 mg/m³, 2003	(reference.html#)
Occupational Exposure Limit-UNITED KINGDOM	time-weighted average 0.1 mg/m³, OCT2007	(reference.html#)
Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (Construction)	8H time-weighted average 0.01 mg(Ag)/m³	CFRGBR (reference.html#CFRGBR) 29.1926.55.1994

(Construction)	mg(Ag)/m	29,1926.55,1994
Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (Federal Contractors)	8H time-weighted average 0.01 mg(Ag)/m^3	CFRGBR (reference.html#CFRGBR) 41,50-204.50,1994
Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (General Industry)	8H time-weighted average 0.01 mg(Ag)/m^3	CFRGBR (reference.html#CFRGBR) 29,1910.1000,1994
Occupational Safety and Health Administration (OSHA) Permissible Exposure Limit (Shipyards)	8H time-weighted average 0.01 mg(Ag)/m^3	CFRGBR (reference.html#CFRGBR) 29,1915.1000,1993

NIOSH Documentation and Surveillance

Organization	Standard	Reference
National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Level TO SILVER, metal and soluble compds-air	10H time-weighted average 0.01 mg/m^3	NIOSH* (reference.html#NIOSH*) DHHS #92-100,1992
National Occupational Exposure Survey 1983	Hazard Code M1804; Number of Industries 4; Total Number of Facilities 156; Number of Occupations 9; Total Number of Employees Exposed 3937; Total Number of Female Employees Exposed 2435	(reference.html#)
National Occupational Exposure Survey 1983	Hazard Code 68730; Number of Industries 118; Total Number of Facilities 13582; Number of Occupations 76; Total Number of Employees Exposed 204921; Total Number of Female Employees Exposed 37439	(reference.html#)
National Occupational Hazard Survey 1974	Hazard Code 68730; Number of Industries 53; Total Number of Facilities 2163; Number of Occupations 54; Total Number of Employees Exposed 19343	(reference.html#)

Status in Federal Agencies

Organization	Reference
ATSDR TOXICOLOGY PROFILE (NTIS** PB/91/180430/AS)	(reference.html#)
EPA TSCA Section 8(b) CHEMICAL INVENTORY	(reference.html#)
EPA TSCA Section 8(d) unpublished health/safety studies	(reference.html#)

EPA TSCA Section 8(d) unpublished health/safety studies	(reference.html#)
EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JANUARY 2001	(reference.html#)
NIOSH Analytical Method, 1994: Elements by ICP, 7300	(reference.html#)
NIOSH Analytical Method, 1994: Elements in blood or tissue, 8005	(reference.html#)
NIOSH Analytical Method, 1994: Metals in urine, 8310	(reference.html#)
On EPA IRIS database	(reference.html#)
OSHA ANALYTICAL METHOD #ID121	(reference.html#)

Page last reviewed: March 7, 2014

Page last updated: May 5, 2016

Content source: National Institute for Occupational Safety and Health (NIOSH) (/niosh/) Education and Information Division

Silver; CASRN 7440-22-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Silver

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	12/01/1991
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	06/01/1989

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 12/01/1991

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of

information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Argyria **2- to 9-Year Human i.v. Study** **Gaul and Staud, 1935**	NOEL: None LOAEL: 1 g (total dose); converted to an oral dose of 0.014 mg/kg/day	3	1	5E-3 mg/kg/day

* Conversion Factors: Based on conversion from the total i.v. dose to a total oral dose of 25 g (i.v. dose of 1 g divided by 0.04, assumed oral retention factor; see Furchner et al., 1968 in Additional Comments section) and dividing by 70 kg (adult body weight) and 25,500 days (a lifetime, or 70 years).

I.A.2. Principal and Supporting Studies (Oral RfD)

Gaul, L.E. and A.H. Staud. 1935. Clinical spectroscopy. Seventy cases of generalized argyrosis following organic and colloidal silver medication. J. Am. Med. Assoc. 104: 1387-1390.

The critical effect in humans ingesting silver is argyria, a medically benign but permanent bluish-gray discoloration of the skin. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. Although silver has been shown to be uniformly deposited in exposed and unexposed areas, the increased pigmentation becomes more pronounced in areas exposed to sunlight due to photoactivated reduction of the metal. Although the deposition of silver is permanent, it is not associated with any adverse health effects. No pathologic changes or inflammatory reactions have been shown to result from silver deposition. Silver compounds have been employed for medical uses for centuries. In the nineteenth and early twentieth centuries, silver arsphenamine was used in the treatment of syphillis; more recently it has been used as an astringent in topical preparations. While argyria occurred more commonly before the development of antibiotics, it is now a rare occurrence. Greene and Su (1987) have published a review of argyria.

Gaul and Staud (1935) reported 70 cases of generalized argyria following organic and colloidal silver medication, including 13 cases of generalized argyria following intravenous silver arsphenamine injection therapy and a biospectrometric analysis of 10 cases of generalized argyria classified according to the quantity of silver present. In the i.v. study, data were presented for 10 males (23-64 years old) and for two females (23 and 49 years old) who were administered 31-100 i.v. injections of silver arsphenamine (total dose was 4-20 g) over a 2- to 9.75-year period. Argyria developed after a total dose of 4, 7 or 8 g in some patients, while in others, argyria did not develop until after a total dose of 10, 15 or 20 g. In the biospectrometric analysis of skin biopsies from 10 cases of generalized argyria, the authors confirmed that the degree of the discoloration is directly dependent on the amount of silver present. The authors concluded that argyria may become clinically apparent after a total accumulated i.v. dose of approximately 8 g of silver arsphenamine. The book entitled "Argyria. The Pharmacology of Silver" reached the same conclusion, that a total accumulative i.v. dose of 8 gm silver arsphenamine is the limit beyond which argyria may develop (Hill and Pillsbury, 1939). However, since body accumulates silver throughout life, it is theoretically possible for amounts less than this (for example, 4 g silver arsphenamine) to result in argyria. Therefore, based on cases presented in this study, the lowest i.v. dose resulting in argyria in one patient, 1 g metallic silver (4 g silver arsphenamine x 0.23, the fraction of silver in silver arsphenamine) is considered to be a minimal effect level for this study.

Blumberg and Carey (1934) reported argyria in an emaciated chronically ill (more than 15 years) 33-year-old female (32.7 kg) who had ingested capsules containing silver nitrate over a period of 1 year. The patient reported ingesting 16 mg silver nitrate three times a day (about 30 mg silver/day) for alternate periods of 2 weeks. Spectrographic analysis of blood samples revealed a blood silver level of 0.5 mg/L 1 week after ingestion of silver nitrate capsules ceased, and there was only a small decrease in this level after 3 months. The authors noted that this marked argyremia was striking because even in cases of documented argyria, blood silver levels are not generally elevated to this extent. Normal levels for argyremic patients were reported to range from not detected to 0.005 mg Ag/l blood. Heavy traces of silver in the skin, moderate amounts in the urine and feces, and trace amounts in the saliva were reported in samples tested 3 months after ingestion of the capsules stopped; however, despite the marked argyremia and detection of silver in the skin, the argyria at 3 months was quite mild. No obvious dark pigmentation was seen other than gingival lines which are considered to be characteristic of the first signs of argyria. The authors suggested that this may have been because the woman was not exposed to strong light during the period of silver treatment. This study is not suitable to serve as the basis for a quantitative risk assessment for silver because it is a clinical report on only one patient of compromised health. Furthermore, the actual amount of silver ingested is based on the patient's recollection and cannot be accurately determined.

In a case reported by East et al. (1980), argyria was diagnosed in a 47-year- old woman (58.6 kg) who had taken excessively large oral doses of anti-smoking lozenges containing silver acetate over a period of 2.5 years. No information was provided as to the actual amount of silver ingested. Symptoms of argyria appeared after the first 6 months of exposure. Based on whole body neutron activation analysis, the total body burden of silver in this female was estimated to be 6.4 (plus or minus 2) g. Both the total body burden and concentration of silver in the skin were estimated to be 8000 times higher than normal. In a separate 30-week experiment, the same subject retained 18% of a single dose of orally-administered silver, a retention level much higher than that reported by other investigators. East et al. (1980) cited other studies on this particular anti-smoking formulation (on the market since 1973) which demonstrated that "within the limits of experimental error, no silver is retained after oral administration." However, this may not hold true for excessive intakes like that ingested by this individual. As with the study by Blumberg and Carey (1934), this study is not suitable to serve as the basis for a quantitative risk assessment. It is a clinical report on only one patient and the actual amount of silver ingested can only be estimated.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — An uncertainty factor of 3 is applied to account for minimal effects in a subpopulation which has exhibited an increased propensity for the development of argyria. The critical effect observed is a cosmetic effect, with no associated adverse health effects. Also, the critical study reports on only 1 individual who developed argyria following an i.v. dose of 1 g silver (4 g silver arsphenamine). Other individuals did not respond until levels five times higher were administered. No uncertainty factor for less than chronic to chronic duration is needed because the dose has been apportioned over a lifetime of 70 years.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

In the study by East et al. (1980) (see section 1.A.2.), one human was found to retain 18% of a single oral dose. However, the authors acknowledge that this high level of retention is not consistent with data published in other laboratories. For ethical reasons, the experiment could be not repeated to determine the validity of the results.

Humans are exposed to small amounts of silver from dietary sources. The oral intake of silver from a typical diet has been estimated to range from 27-88 ug/day (Hamilton and Minski, 1972/1973; Kehoe et al., 1940). Tipton et al. (1966) estimated a lesser intake of 10-20 ug/day in two subjects during a 30- day observation period. Over a lifetime, a small but measurable amount of silver is accumulated by individuals having no excessive exposure. Gaul and Staud

(1935) estimated that a person aged 50 years would have an average retention of 0.23-0.48 g silver (equivalent to 1-2 g silver arsphenamine). Petering et al. (1991) estimated a much lower body burden of 9 mg over a 50- year period based on estimated intake, absorption, and excretion values; however, it is not clear how the final estimate was calculated. Furchner et al. (1968) studied the absorption and retention of ingested silver (as silver nitrate, amount not specified) in mice, rats, monkeys and dogs. In all four species, very little silver was absorbed from the GI tract. Cumulative excretion ranged from 90 to 99% on the second day after ingestion, with <1% of the dose being retained in <1 week in monkeys, rats and mice. Dogs had a slightly greater retention. The authors used the data from the dog to estimate how much silver ingested by a 70 kg human would be retained. An "equilibrium factor" of 4.4% was determined by integrating from zero to infinity a retention equation which assumes a triphasic elimination pattern for silver with the initial elimination of 90% coming from the dog data. The first elimination half-time of 0.5 days was used "arbitrarily"; subsequent half-times of 3.5 days and 41 days were taken from a metabolic study by Polachek et al. (1960). Furchner et al. (1968) considered their calculated equilibrium factor of 4.4% to be a conservative estimate for the amount of silver which would be retained by a 70 kg human. This figure was rounded to 4% and was used in the dose conversion (i.v. dose converted to oral intake) for the calculation of the RfD.

In addition to silver arsphenamine, any silver compound (silver nitrate, silver acetate, argyrol, Neosilvol and Collargol, etc.), at high dose, can cause argyria. Another important factor predisposing to the development of argyria is the exposure of the skin to light.

Argyria, the critical effect upon which the RfD for silver is based, occurs at levels of exposure much lower than those levels associated with other effects of silver. Argyrosis, resulting from the deposition of silver in the eye, has also been documented, but generally involves the use of eye drops or make-up containing silver (Greene and Su, 1987). Silver has been found to be deposited in the cornea and the anterior capsule of the lens. The same deposition pattern was seen in the eyes of male Wistar rats following administration of a 0.66% silver nitrate solution to the eyes for 45 days (Rungby, 1986). No toxicological effects were reported.

Toxic effects of silver have been reported primarily for the cardiovascular and hepatic systems. Olcott (1950) administered 0.1% silver nitrate in drinking water to rats for 218 days. This exposure (about 89 mg/kg/day) resulted in a statistically significant increase in the incidence of ventricular hypertrophy. Upon autopsy, advanced pigmentation was observed in body organs, but the ventricular hypertrophy was not attributed to silver deposition.

Hepatic necrosis and ultrastructural changes of the liver have been induced by silver administration to vitamin E and/or selenium deficient rats (Wagner et al., 1975; Diplock et al., 1967; Bunyan et al., 1968). Investigators have hypothesized that this toxicity is related to a silver-induced selenium deficiency that inhibits the synthesis of the seleno-enzyme glutathione

peroxidase. In animals supplemented with selenium and/or vitamin E, exposures of silver as high as 140 mg/kg/day (100 mg Ag/L drinking water) were well- tolerated (Bunyan et al., 1968).

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Low
RfD — Low

The critical human study rates a medium confidence. It is an old study (1935) which offers fairly specific information regarding the total dose of silver injected over a stated period of time. One shortcoming of the study is that only patients developing argyria are described; no information is presented on patients who received multiple injections of silver arsphenamine without developing argyria. Therefore, it is difficult to establish a NOAEL. Also, the individuals in the study were being treated for syphilis and may have been of compromised health.

Confidence in the database is considered to be low because the studies used to support the RfD were not controlled studies. For clinical case studies of argyria (such as Blumberg and Carey, 1934; East et al., 1980), it is especially difficult to determine the amount of silver that was ingested.

Confidence in the RfD can be considered low-to-medium because, while the critical effect has been demonstrated in humans following oral administration of silver, the quantitative risk estimate is based on a study utilizing intravenous administration and thus necessitates a dose conversion with inherent uncertainties.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — None

Agency Work Group Review — 10/09/1985, 02/05/1986, 04/18/1990, 02/20/1991, 07/18/1991

Verification Date — 07/18/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for silver conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new

studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Silver
CASRN — 7440-22-4

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 06/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classified as to human carcinogenicity

Basis — In animals, local sarcomas have been induced after implantation of foils and discs of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas.

II.A.2. Human Carcinogenicity Data

No evidence of cancer in humans has been reported despite frequent therapeutic use of the compound over the years.

II.A.3. Animal Carcinogenicity Data

Inadequate. Local sarcomas have been induced after subcutaneous (s.c.) implantation of foils and discs of silver and other noble metals. Furst (1979, 1981), however, cited studies showing that even insoluble solids such as smooth ivory and plastic result in local fibrosarcomas and that tin when crumbled will not. He concluded that i.p. and s.c. implants are invalid as indicators of carcinogenicity because a phenomenon called solid-state carcinogenesis may complicate the interpretation of the cause of these tumors. It is difficult to interpret these implantation site tumors in laboratory animals in terms of exposure to humans via ingestion. Within these constraints there are two studies given below in which silver per se appeared to induce no carcinogenic response.

Schmahl and Steinhoff (1960) reported, in a study of silver and of gold, that colloidal silver injected both i.v. and s.c. into rats resulted in tumors in 8 of 26 rats which survived longer than 14 months. In 6 of the 8, the tumor was at the site of the s.c. injection. In about 700 untreated rats the rate of spontaneous tumor formation of any site was 1 to 3%. No vehicle control was reported.

Furst and Schlauder (1977) evaluated silver and gold for carcinogenicity in a study designed to avoid solid-state carcinogenesis. Metal powder was suspended in trioctanoin and injected monthly, i.m., into 50 male and female Fischer 344 rats per group. The dose was 5 mg each for 5 treatments and 10 mg each for 5 more treatments for a total dose of 75 mg silver. The treatment regimen included a vehicle control (a reportedly inert material), and cadmium as a positive control. Injection site sarcomas were found only in vehicle control (1/50), gold (1/50) and

cadmium (30/50); no tumors (0/50) appeared at the site of injection in the silver-treated animals. A complete necropsy was performed on all animals. The authors mentioned the existence of spontaneous tumors in Fischer 344 rats, but reported only injection site tumors. They concluded that finely divided silver powder injected i.m. does not induce cancer.

II.A.4. Supporting Data for Carcinogenicity

Further support for the lack of silver's ability to induce or promote cancer stems from the finding that, despite long standing and frequent therapeutic usage in humans, there are no reports of cancer associated with silver. In a recent Proceedings of a Workshop/Conference on the Role of Metals in Carcinogenesis (1981) containing 24 articles on animal bioassays, epidemiology, biochemistry, mutagenicity, and enhancement and inhibition of carcinogenesis, silver was not included as a metal of carcinogenic concern.

No evidence of the mutagenicity of silver was shown in two available studies. Demerec et al. (1951) studied silver nitrate for the possible induction of back-mutations from streptomycin dependence to nondependence in Eschericha coli. Silver nitrate was considered nonmutagenic in this assay. Nishioka (1975) screened silver chloride with other chemicals for mutagenic effects using a method called the rec-assay. Silver chloride was considered nonmutagenic in this assay.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1988

The 1988 Drinking Water Criteria Document for Silver has received Agency Review.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 09/22/1988

Verification Date — 09/22/1988

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for silver conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Silver
CASRN — 7440-22-4

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Silver
CASRN — 7440-22-4

Date	Section	Description
06/01/1989	II.	Carcinogen summary on-line
08/01/1991	I.A.	Withdrawn; new oral RfD verified (in preparation)
12/01/1991	I.A.	Oral RfD summary replaced; RfD changed
10/28/2003	I.A.6, II.D.2	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Silver
CASRN — 7440-22-4
Last Revised — 06/01/1989

- 7440-22-4
- ARGENTUM CREDE
- COLLARGOL
- Silver

The following information was generated from the
Hazardous Substances Data Bank (HSDB),
a database of the National Library of Medicine's TOXNET system
(http://toxnet.nlm.nih.gov) on July 19, 2016.

Query: Records containing the term 7440 22 4

1 - HSDB
NAME: SILVER, ELEMENTAL

HSN: 5034

RN: 7440-22-4

NOTE:
This record contains information for silver in its zero valence state only. For general toxicity and environmental fate of silver ions and silver compounds, refer to the SILVER COMPOUNDS record; for compound specific information, refer to the appropriate individual records, e.g., silver nitrate, silver iodide, etc.

OVERVIEW:

HUMAN HEALTH EFFECTS:

EVIDENCE FOR CARCINOGENICITY:
Cancer Classification: Group D Not Classifiable as to Human Carcinogenicity[USEPA Office of Pesticide Programs, Health Effects Division, Science Information Management Branch: "Chemicals Evaluated for Carcinogenic Potential" (April 2006)] **QC REVIEWED**

CLASSIFICATION: D; not classifiable as to human carcinogenicity. BASIS FOR CLASSIFICATION: In animals local sarcomas have been induced after implantation of foils and disks of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas. ANIMAL CARCINOGENICITY DATA: Inadequate .[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on Silver (7440-22-4). Available from, as of March 15, 2000: http://www.epa.gov/iris/] **PEER REVIEWED**

HUMAN TOXICITY EXCERPTS:
IN INDUSTRY ARGYRIA FOLLOWING EXPOSURE TO SILVER MAY BE LOCALIZED OR GENERALIZED. LOCALIZED FORM OCCURS CHIEFLY DURING HANDLING OF METALLIC SILVER, WHEN PARTICLES BECOME IMBEDDED IN SKIN & SC TISSUES, EYE LESIONS MAY ALSO BE MANIFESTATION. ...[Browning, E. Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 298] **PEER REVIEWED**

A LOCALIZED BLACKISH DISCOLORATION & /TISSUE MASS/ OF CONJUNCTIVA DEVELOPED IN PATIENT'S EYE MANY YEARS AFTER SMALL SILVER INSTRUMENT HAD BEEN ACCIDENTALLY LEFT IN TISSUES AT SITE OF OPERATION FOR STRABISMUS.[Grant, W. M. Toxicology of the Eye. 2nd ed. Springfield, Illinois: Charles C. Thomas, 1974., p. 910] **PEER REVIEWED**

... Formation of a meningioma was found surrounding a silver clip left from an operation two years before to remove an ependymoma in the brain of an eleven year old girl.[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-114 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Silver concentrations in human tissues apparently increase with age. It has been detected in fetal livers and placentae.[Robkin MA et al; Trans Am Nucl Soc 17: 97 (1973) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-1 (1980) EPA 440/5-80-071] **PEER REVIEWED**

A striking feature of argyria is the regular deposition of silver in blood vessels and connective tissue, especially around the face, conjunctiva, hands, and fingernails.[Hill WR Pillsbury DM; Argyia, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-42 (1980) EPA 440/5-80-071] **PEER REVIEWED**

A nephrotic syndrome in an obese, argyric 73 yr old man was attributed to silver deposits in the kidney. The man had used a silver containing mouthwash or gargle for 10 years (1955-1965), presumably corresponding to the absorption of a total amount of 88 g of silver. The patient showed respiratory insufficiency and a nephrotic syndrome with proteinuria, elevated alpha-2 macroglobulins, and glomerular (but not tubular) involvement. Silver deposits were found in the glomerular basement membrane.[Zech P et al; Nouv Presse Med 2: 161 (1973) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-79 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Collargol was used /iv/ to fill the renal pelvis for X-ray study and resulted in severe hemorrhagic diathesis with parenchymatous hemorrhages in the stomach, intestines, and body cavities ending in death. /Argyrol/[Hill WR, Pillsbury DM; Argyria, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-69 (1980) EPA 440/5-80-071] **PEER REVIEWED**

METALLIC SILVER MAY BE INHALED BY SILVER FINISHERS LEADING TO ABNORMAL CHEST X-RAY FINDINGS. ... ITS IMPORTANCE LIES IN FAILURE TO RECOGNIZE CAUSE OF SUCH X-RAY CHANGES RESULTING IN UNNECESSARY DIAGNOSTIC STUDIES OR EXCLUSION FROM EMPLOYMENT.[Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974., p. 171] **PEER REVIEWED**

... DEVELOPMENT /OF ARGYRIA (POISONING BY SILVER OR A SILVER SALT WHICH LEADS TO A PERMANENT ASHEN-GRAY DISCOLORATION OF THE SKIN, CONJUNCTIVA, AND INTERNAL ORGANS)/ FROM INHALATION THROUGH OCCUPATIONAL EXPOSURE APPEARS TO BE VERY SLOW & MAY REQUIRE YEARS.[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values, 4th ed., 1980. Cincinnati, Ohio: American Conference of Governmmental Industrial Hygienists, Inc., 1980., p. 367] **PEER

REVIEWED**

There is no evidence that silver or its compounds are carcinogenic to man.[Clayton, G. D. and F. E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology: Volume 2A, 2B, 2C: Toxicology. 3rd ed. New York: John Wiley Sons, 1981-1982., p. 1888] **PEER REVIEWED**

Silver in metallic form is harmless with the possible exception of colloidal silver preparations.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 922] **PEER REVIEWED**

Silver may be a cause of metal fume fever.[Haddad, L.M. and Winchester, J.F. Clinical Management of Poisoning and Drug Overdosage. Philadelphia, PA: W.B. Saunders Co., 1983., p. 662] **PEER REVIEWED**

High local concn of silver from a prosthetic cement were associated with a slowly resolving focal neuropathy.[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1060] **PEER REVIEWED**

10 cc of a 2% solution were administered intravenously (Collargol). Survival time was five minutes resulting in cyanosis, coma; death due to pulmonary edema. There was no silver found in the lung.[Hill WR, Pillsbury DM; Argyria, the Pharmacology of Silver (1939) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-69 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Case reports were cited for four radiographers who were placed in danger due to the x-ray processing chemical fumes present in their workspace. These four cases encompass nearly all the 19 symptoms which have been associated with reactions to chemical fumes: severe headaches, sore throat/hoarseness, nasal discharge, sore eyes, unexpected fatigue, sinus problems, nausea, painful joints, bad taste in mouth, mouth ulcers, catarrh, tinnitus, tight chest, skin rash, lip sores, shortness of breath, unusual heart rhythms, chest pains, and numb extremities. Three of the four workers eventually had to give up work in radiography, and continued to experience sensitivity to radiographic chemicals and other substances such as automotive exhausts, cigarette smoke, paint fumes and red wine. The fourth radiographer was engaged in silver recovery starting in 1958; he suffered upper respiratory symptoms and recurring bouts of unexplained pneumonia starting in 1970 until 1983 when he started to use a full face mask and canister during silver recovery.[Gordon M; Radiography 53 (608): 85-9 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3685272?dopt=Abstract" target=new>PubMed Abstract

A cross sectional study was conducted on workers engaged in manufacturing precious metal powder. Of the 27 workers, 96% had elevated urine silver concentrations and 92% had elevated blood silver concentrations. Most workers had symptoms of respiratory irritation and nose bleeds were reported in 8 workers. Deposition of silver in the cornea of the eye was detected in 5 of 8 of the long term workers. The urinary enzyme

N-acetyl-B-D glucosaminidase was significantly elevated in 4 individuals and was correlated with blood silver concentrations and age.[Rosenman KD et al; Brit J Indust Med 44 (4): 267-72 (1987)] **PEER REVIEWED**

It has been postulated that nickel/cobalt and nickel/palladium exhibit coreactivity in patients allergic to metals. OBJECTIVES: (1) Determine the incidence rate and the source for the induction of metal allergy in 3 groups of men: unpierced, one site pierced, and multiple sites pierced; and (2) evaluate the degree of coreactivity between nickel/cobalt and nickel /palladium. ... The source of the induction of the allergic accounted for 5 of 6 nickel allergies and 2 of 3 gold allergies. Silver jewelry was a significant predictor of an allergic response.[Enrlich A et al; Am J Contact Dermat 12 (3): 151-5 (2001)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11526520?dopt=Abstract" target=new>PubMed Abstract

OBJECTIVE: Discoloration of the oral mucosa due to amalgam may appear histologically merely as brown pigmentation of the fibrous extracellular matrix. It was the aim of these investigations to identify the fibrous component that contains silver granules. METHODS: Biopsy specimens from seven patients with clinically diagnosed amalgam tattoos were investigated by light and electron microscopy as well as by X-ray microanalysis. RESULTS: Light microscopy revealed small brown discolored fibers in all specimens; in sections stained with Weigert's resorcinfuchsin, they appeared dark violet. Scanning electron microscopy revealed metallic granules associated with thin fibers; by X-ray microanalysis, they exhibited preferentially peaks for silver and sulfur. Transmission electron microscopy detected only electron-dense particles in elastic fibers. CONCLUSIONS: With the different morphological methods, silver granules of amalgam tattoos were exclusively detected within elastic fibers. This result indicates that granular brown discoloration of the matrix fibrils is due to silver impregnation of elastic fibers. Therefore, the histopathological diagnosis of amalgam tattoo is possible even in the absence of larger amalgam particles with black appearance.[Mohr W, Gorz E et al; HNO 49 (6): 454-7 (2001)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11450512?dopt=Abstract" target=new>PubMed Abstract

A St. Jude Medical Silzone was implanted in a 72-year-old female, suffering from mitral valve disease. Four months later, the patient had acute cardiac failure due to partial detachment of the prosthetic valve. The mitral annulus was ulcerated and there were multiple erosions in the myocardial tissue in contact with the prosthetic valve. Histological examination revealed chronic inflammation with hemosiderine deposits and giant cells. No allergy to silver ions was found. The silver-coated sewing cuff had caused a chronic inflammatory reaction due to a toxic reaction to silver. The Silzone valve was withdrawn from the market on January 2000.[Tozzi P et al; Eur J Cardiothorac Surg 19 (5): 729-31 (2001)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11343965?dopt=Abstract" target=new>PubMed Abstract

Silver metal and soluble silver compounds can cause discoloration or blue-grey darkening of the eyes, nose, throat, and skin. /Silver metal

& sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1] **PEER REVIEWED**

Potential symptoms as a result of exposure /to silver, metal, and sol cmpd (as Ag)/: Blue-gray eye, nasal septum, throat, skin; irritation skin, ulceration; GI. /Silver, metal, and sol cmpd (as Ag)/[NIOSH. Pocket Guide to Chemical Hazards. 5th Printing/Revision. DHHS (NIOSH) Publ. No. 85-114. Washington, D.C.: U.S. Dept. of Health and Human Services, NIOSH/Supt. of Documents, GPO, Sept. 1985., p. 209] **PEER REVIEWED**

The organs which are affected by exposure to silver, metal, and sol cmpd (as Ag) are nasal septum, skin, eyes. /Silver, metal, and sol cmpd (as Ag)/[NIOSH. Pocket Guide to Chemical Hazards. 5th Printing/Revision. DHHS (NIOSH) Publ. No. 85-114. Washington, D.C.: U.S. Dept. of Health and Human Services, NIOSH/Supt. of Documents, GPO, Sept. 1985., p. 209] **PEER REVIEWED**

... DEVELOPMENT /OF ARGYRIA (POISONING BY SILVER OR A SILVER SALT WHICH LEADS TO A PERMANENT ASHEN-GRAY DISCOLORATION OF THE SKIN, CONJUNCTIVA, AND INTERNAL ORGANS)/ FROM INHALATION THROUGH OCCUPATIONAL EXPOSURE APPEARS TO BE VERY SLOW & MAY REQUIRE YEARS.[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values, 4th ed., 1980. Cincinnati, Ohio: American Conference of Governmmental Industrial Hygienists, Inc., 1980., p. 367] **PEER REVIEWED**

... A large number of case reports of argyria, mostly resulting from the use of silver compounds in medical treatment by injection (silver arsphenamine) or by oral admin (silver nitrate) /were examined/. /It was/ concluded that the lowest total doses to produce argyria were the admin of 1 g of elemental silver by injection or 1.4 g after ingestion of small amounts each day over several months. /Silver and silver compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1398] **PEER REVIEWED**

A great many case reports of argyria associated with ingestion of silver-containing breath mints, antacids, & lozenges have been published. Chronic use of silver-containing nose drops & topical application of silver nitrate to mucous membranes have also caused argyria. Direct ocular or dermal contact with concentrated silver nitrate solutions resulted in chemical burns. /Silver and silver compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**

A cross-sectional study of workers producing precious-metal powder showed a significant decr in creatinine clearance in those exposed to silver, though this may have been due to the confounding effect of cadmium. /Silver powder/[Rom, W.N. (ed.). Environmental and Occupational Medicine.

2nd ed. Boston, MA: Little, Brown and Company, 1992., p. 822] **PEER REVIEWED**

The staining of skin by silver is termed argyria and is grey-blue in colour. This may be caused by a number of mechanisms such as ingestion and direct implantation. We report an unusual case, caused by an impacted earring, where the skin discoloration was not entirely typical of argyria. This may have been due to copper impurities present in the earring.[Sugden P et al; Br J Plast Surg 54 (3): 252-3 (2001)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11254422?dopt=Abstract" target=new>PubMed Abstract

In one case report of a worker who had become ill 14 hr after he had been working with molten silver ingots, symptoms were limited primarily to the respiratory system ... . Unfortunately, the concn and chemical comp of the silver in the work room air were not known, and the history of exposure to silver prior to this incident was not reported. The initial symptoms seen in this patient incl audible crackles during breathing, rapid pulse, low oxygen content of capillary blood, and scattered thickening of the lungs observed in chest radiograms. The patient's symptoms progressed to acute respiratory failure, from which the patient eventually recovered fully. /Silver/[DHHS/ATSDR; Toxicological Profile for Silver p. 13 TP-90-24 (1990)] **PEER REVIEWED**

MEDICAL SURVEILLANCE:

Skin examination. Fecal silver level. /From Table/[Fuscaldo, A., B. J. Erlick, and B. Hindman. (eds.). Laboratory Safety-Theory and Practice. New York: Academic Press, 1980., p. 267] **PEER REVIEWED**

Special attention should be given to other sources of silver exposure, for example, medications, or previous occupational exposure. Inspection of the nasal septum, eyes, and throat will generally give incidence of pigmentation before generalized argyria occurs. This will usually be seen first in the ear lobes, face, and hands.[Sittig, M. Handbook of Toxic and Hazardous Chemicals and Carcinogens, 1985. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 1985., p. 789] **PEER REVIEWED**

Discoloration of Descemet's membrane by silver has been said to be the most sensitive indicator of chronic exposure to silver, and the suggestion has been made that silver workers be examined routinely with a slitlamp biomicroscope for early detection of argyrosis before other manifestations become evident. ... Others have reported that the initial signs of occupational argyrosis were more likely to appear in the conjunctiva than in the cornea.[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 814] **PEER REVIEWED**

The assessment of silver exposure can be accomplished by measurement of silver. This measurement may be useful for identification of recent exposure, but not for assessing chronic exposure. Whole Blood Reference Ranges: Normal - Less than 5 ug/l. Exposed - Not established. Toxic - Not established.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1084] **PEER REVIEWED**

The literature search did not reveal reports of monitoring tests for assessment of silver absorption. Serum or Plasma Reference Ranges: Normal = Not established. Exposed = Not established. Toxic = Not established.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1084] **PEER REVIEWED**

The assessment of silver exposure can be accomplished through measurement of silver, which has been demonstrated to correlate well with environmental exposure levels. Levels of silver in urine may be useful for identification of recent exposure (in the last week or so); however, it is not as useful for assessment of chronic exposure as compared to looking for silver in the skin. Urine Reference Ranges: Normal - Less than 1.0 ug/24 hours. Exposed - Exposure to air levels from 0.27 to 60 mg/cu m yielded urinary values of 5 to 261 ug/24 hour, with a mean of 27 ug/24 hours after a 5 day period. Toxic - Not established.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1084] **PEER REVIEWED**

Respiratory Symptom Questionnaires: Questionnaires published by the American Thoracic Society (ATS) and the British Medical Research Council have proven useful for identifying people with chronic bronchitis. Certain pulmonary function tests such as the FEV1 have been found to be better predictors of chronic airflow obstruction.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1085] **PEER REVIEWED**

Chest Radiography: Chest radiographs are widely used to assess pulmonary disease. They are useful for detecting early lung cancer in asymptomatic people, and especially for detecting peripheral tumors such as adenocarcinomas. However, even though OSHA mandates this test for exposure to some toxicants such as asbestos, experts' views on the risk to benefit ratio in detection of pulmonary disease conflict, so routine annual chest X-rays are not recommended for all people.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1085] **PEER REVIEWED**

Pulmonary Function Tests: The tests that have been found to be practical for population monitoring include: Spirometry and expiratory flow-volume curves; Determination of lung volumes; Diffusing capacity for carbon monoxide; Single-breath nitrogen washout; Inhalation challenge tests; Serial measurements of peak expiratory flow; Exercise testing.[Ryan, R.P., C.E. Terry, S.S. Leffingwell (eds.) Toxicology Desk Reference 5th ed. Volumes 1-2. Taylor & Francis Philadelphia, PA. 2000, p. 1085] **PEER REVIEWED**

The following medical procedures should be made available to each employee who is exposed to silver metal & sol silver cmpd at potentially hazardous levels: 1. Initial medical exam: Exam of the nasal septum, eyes, and skin for evidence of pigmentation: The purpose is to establish a baseline for future observations of silver deposition in tissues. 2. Periodic medical exam: The aforementioned medical exam should be repeated on an annual basis. /Silver metal & sol silver cmpd/[Mackison, F. W.,

R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 1] **PEER REVIEWED**

Workers exposed to silver & silver salts should be examined routinely for early signs of argyria by inspecting their eyes, nasal & buccal mucosa, ear-lobes, face & hands. There are no established biologic monitoring techniques for silver. /Silver and silver salts/[Rom, W.N. (ed.). Environmental and Occupational Medicine. 2nd ed. Boston, MA: Little, Brown and Company, 1992., p. 823] **PEER REVIEWED**

POPULATIONS AT SPECIAL RISK:

Blond people are considered more susceptible to argyria than others.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 622] **PEER REVIEWED**

PROBABLE ROUTES OF HUMAN EXPOSURE:

Silver may be released from silver amalgam dental fillings when placed in unlined cavities ...[Leirskar J; Scand J Dent Res 82: 74 (1974) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-21 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Where men work with metallic silver, small particles may accidentally penetrate the exposed skin. ... This may occur in occupations involving the filing, drilling, hammering, turning, engraving, polishing, forging, soldering & smelting of silver.[International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983., p. 2047] **PEER REVIEWED**

METALLIC SILVER MAY BE INHALED BY SILVER FINISHERS LEADING TO ABNORMAL CHEST X-RAY FINDINGS.[Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974., p. 171] **PEER REVIEWED**

BODY BURDEN:

Urine samples collected from six males, aged 28 to 51 years, who had been employed in jewelry handicraft for 7 to 23 years, were analyzed for silver. Urinary silver ranged from 5 to 261 micrograms per 24 hours. A mean value of about 27 micrograms was found after shifts over 5 days in workers performing investment casting with oxyacetylene flame, while the mean urinary silver level in workers performing the electromagnetic induction process was about 5 micrograms after shifts.[Minoia C et al; Occupational and Environmental Chemical Hazards p.349-54 (1987)] **PEER REVIEWED**

EMERGENCY MEDICAL TREATMENT:

EMERGENCY MEDICAL TREATMENT:

LIFE SUPPORT:

o This overview assumes that basic life support measures have been instituted.

CLINICAL EFFECTS:

0.2.1 SUMMARY OF EXPOSURE

0.2.1.1 ACUTE EXPOSURE

A) USES: Silver is a natural element used in the manufacturing of ornaments, jewelry, utensils and industrial manufacturing. In addition, silver compounds are used in film processing, disinfectants, and microbiocides (eg, silver sulfadiazine). Colloidal silver is manufactured by suspending silver particles in a liquid, which is sold as a dietary supplement and homeopathic remedy.

B) PHARMACOLOGY: Silver has no known biological functions in humans. Silver sulfadiazine is bacteriostatic; it competitively inhibits bacterial or fungal dihydropteroate synthetase, preventing PABA conversion to folic acid. Upon contact with skin surface, silver sulfadiazine separates into sulfadiazine and silver, and the silver is absorbed into the blood circulation.

C) TOXICOLOGY: Other than argyria, systemic silver toxicity is rare due to rapid binding of silver to various proteins and precipitation of silver chloride. Tissue damage only occurs when this binding ability is overwhelmed by a massive dose.

D) EPIDEMIOLOGY: Hundreds of exposures to silver (colloidal and silver compounds such as silver nitrate and silver oxide batteries) are reported to poison centers every year. Exposures rarely cause significant symptoms and are never fatal.

E) WITH THERAPEUTIC USE

1) ADVERSE EFFECTS: Adverse effects from the us of topical silver preparations such as silver

sulfadiazine include a temporary painful burning sensation and the formation of aseptic exudates on the wound's surface. In addition, hypersensitivity reactions such as urticaria can result from silver exposure. Finally, incorporation of silver ions into the skin can lead to localized argyria, especially in the setting of UV radiation.

F) WITH POISONING/EXPOSURE

1) MILD TO MODERATE TOXICITY: Most patients remain asymptomatic. Patients require chronic exposure for significant absorption to occur. Argyria, a blue-grey discoloration of the skin, mucous membranes, and conjunctiva, cornea, or lens that is not associated with clinical symptoms, can develop after chronic exposure. Silver salts such as silver oxide or silver nitrate are irritating and corrosive. Chronic inhalation has been associated with mild chronic bronchitis. Unusual or rare complications of medicinal treatment with silver or silver salts include leukopenia, anemia, hemorrhage and elevated liver enzymes.

2) SEVERE TOXICITY: One case report exists of a workman exposed to high concentration of heated metallic silver vapor for 4 hours developing acute lung injury with pulmonary edema. There are rare cases of patients with neurologic symptoms after large exposures to silver, including symptoms of peripheral neuropathy, decreased mental status, and seizures.

0.2.4 HEENT

0.2.4.1 ACUTE EXPOSURE

A) Argyria may be generalized or localized to the conjunctiva, cornea, or lens. This blue-grey discoloration is not accompanied by vision loss.

0.2.20 REPRODUCTIVE HAZARDS

A) At the time of this review, no data were found in available references to assess the potential effects of exposure to this agent in humans during pregnancy.

0.2.21 CARCINOGENICITY

0.2.21.1 IARC CATEGORY

A) IARC Carcinogenicity Ratings for CAS7440-22-4 (International Agency for Research on Cancer, 2015; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2008; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2006; IARC, 2004):

1) Not Listed

0.2.21.2 HUMAN OVERVIEW

A) At the time of this review, no studies were found on the possible carcinogenic activity of silver in humans.

0.2.21.3 ANIMAL OVERVIEW

A) Fibrosarcoma developed in 30 percent of rats who had silver foil imbedded in the skin. Silver is considered an equivocal tumorigenic agent by RTECS criteria.

0.2.22 GENOTOXICITY

A) Silver compounds did not cause mutations in S typhimurium or in E coli. It was clastogenic in transformed hamster embryo cells and in cultured Chinese hamster ovary cells.

LABORATORY:

A) No specific studies are needed for most patients.

B) Specific concentrations of silver are not readily available and are unlikely to be useful in the acute setting, but can be used to confirm exposure. A normal serum silver concentration is less than 0.05 mcg/dL.

C) Depending on the patient's presentation and symptoms, other tests may be useful or necessary. Suicidal patients should receive an ECG, basic chemistry panel, and testing for acetaminophen and salicylates, while patients with respiratory distress may need pulse oximetry monitoring and patients with seizures require a thorough neurologic exam and a head CT or MRI.

TREATMENT OVERVIEW:

0.4.2 ORAL EXPOSURE

A) MANAGEMENT OF MILD TO MODERATE TOXICITY

1) For most silver exposures, no treatment is necessary beyond discontinuing exposure. Discoloration with argyria is mostly permanent and there is no good evidence for treatment with local therapies or chelation. Patients with respiratory symptoms can be treated with supplemental oxygen and inhaled beta agonists as needed.

B) MANAGEMENT OF SEVERE TOXICITY

1) Severe toxicity secondary to silver is extremely rare, and consists of supportive care as needed (eg, intubation for severe respiratory distress).

2) INHALATION EXPOSURE: Move patient from toxic environment to fresh air, and monitor and treat for respiratory symptoms as needed.

3) OCULAR EXPOSURE: Remove contact lenses and irrigate exposed eyes with copious amounts of room temperature water for at least 15 minutes. If irritation, pain, swelling, lacrimation or photophobia persists, referral for medical care may be warranted.

4) DERMAL EXPOSURE: Remove contaminated clothing and wash exposed area thoroughly with soap and water. Localized irritation can be treated with standard treatments (eg, topical steroids for hypersensitivity reactions, etc).

C) DECONTAMINATION

1) PREHOSPITAL: GI decontamination is not indicated as absorption is minimal; toxicity has only been reported after long term chronic ingestion. Wash exposed skin with soap and water. There is no evidence for the use of ipecac or prehospital activated charcoal for silver.

2) HOSPITAL: GI decontamination is not indicated as

absorption is minimal; toxicity has only been reported after long term chronic ingestion. Wash exposed skin with soap and water.

D) ANTIDOTE

1) There is no specific antidote.

E) MONITORING OF PATIENT

1) No specific studies are needed for most patients.
2) Specific concentrations of silver are not readily available and are unlikely to be useful in the acute setting, but can be used to confirm exposure. A normal serum silver concentration is less than 0.05 mcg/dL.
3) Depending on the patient's presentation and symptoms, other tests may be useful or necessary. Suicidal patients should receive an ECG, basic chemistry panel, and testing for acetaminophen and salicylates, while patients with respiratory distress may need pulse oximetry monitoring and patients with seizures may require neurology exams and a head CT.

F) ENHANCED ELIMINATION

1) There is no evidence for enhanced elimination techniques. In one case, hemodialysis was ineffective in reducing serum silver concentrations, and plasma exchange and hemofiltration do not significantly reduce the body burden of silver. Chelation therapy has not been successful for treatment because silver is relatively inert after being deposited into tissues.

G) PATIENT DISPOSITION

1) HOME CRITERIA: Patients with mild symptoms that simply require decontamination for treatment may remain at home.
2) OBSERVATION CRITERIA: Patients with persistent or worsening symptoms should be sent to a healthcare facility for evaluation. Patients should be observed until they are stable and symptoms have clearly improved.
3) ADMISSION CRITERIA: Patients exposed to silver or silver compounds should rarely need admission to the hospital. Patients with more severe symptoms (eg, corrosive damage to mucosa membranes from silver salts or seizures may require admission to the hospital for further evaluation or observation). Most patients can be admitted to the hospital ward, but patients with severe symptoms (eg, respiratory distress requiring intubation, seizures) may require ICU care. Patients should remain in the hospital until they are stable and symptoms have clearly improved.
4) CONSULT CRITERIA: Consult a medical toxicologist or poison center for patients with significant toxicity or in whom the diagnosis is unclear.

H) PITFALLS

1) Pitfalls may include using treatments that are ineffective (ie, activated charcoal or chelation) and mistaking argyria for other medical conditions such as cyanosis.

I) PHARMACOKINETICS

1) Topical silver sulfadiazine has approximately 1% systemic silver absorption with approximately 25% of absorbed silver excreted in urine.

J) TOXICOKINETICS

1) Soluble silver salts are absorbed from the respiratory and GI tracts and complex silver slats are absorbed into the blood stream through intact skin. Up to 90 to 99% of oral silver doses are not absorbed. Absorbed silver is strongly retained after deposition into elastic and connective tissues throughout the body. The primary route of excretion is thought to be through bile. In humans, the biological half-life of silver in lungs has been estimated to be 1 day.

K) PREDISPOSING CONDITIONS

1) A patient with renal failure may be more predisposed to toxicity due to partial excretion of silver through urine.

L) DIFFERENTIAL DIAGNOSIS

1) Argyria may be mistaken for cyanosis, methemoglobinemia, metastatic melanoma with melanogenuria, or hemochromatosis.

0.4.3 INHALATION EXPOSURE

A) INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with an inhaled beta2-adrenergic agonist. Consider systemic corticosteroids in patients with significant bronchospasm.

0.4.4 EYE EXPOSURE

A) DECONTAMINATION: Remove contact lenses and irrigate exposed eyes with copious amounts of room temperature 0.9% saline or water for at least 15 minutes. If irritation, pain, swelling, lacrimation, or photophobia persist after 15 minutes of irrigation, the patient should be seen in a healthcare facility.

0.4.5 DERMAL EXPOSURE

A) OVERVIEW

1) DECONTAMINATION: Remove contaminated clothing and jewelry and place them in plastic bags. Wash exposed areas with soap and water for 10 to 15 minutes with gentle sponging to avoid skin breakdown. A physician may need to examine the area if irritation or pain persists (Burgess et al, 1999).

RANGE OF TOXICITY:

A) TOXICITY: Acute toxicity is usually low; toxicity usually occurs following chronic exposure. The estimated average daily intake (from most foods) is 0.088 mg.

B) INGESTION: CHRONIC EXPOSURE: The minimum oral dosage necessary to cause systemic argyria has been estimated to be about 25 to 30 g over 6 months.

C) INHALATION: LACK OF EFFECT: Exposure to silver

concentrations in air of less than 0.01 mg/m(3) has not caused argyria.

ANTIDOTE AND EMERGENCY TREATMENT:

Dimercaptosuccinic acid (DMSA) provides two -SH (sulfhydryl groups) which can chelate heavy metals. ... DMSA is specific for ... silver but does not bind iron, calcium, or magnesium.[Ellenhorn, M.J., S. Schonwald, G. Ordog, J. Wasserberger. Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1997., p. 97] **PEER REVIEWED**

Basic treatment: Establish a patent airway. Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if needed. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary edema and treat if necessary ... . Monitor for shock and treat if necessary ... . Anticipate seizures and treat if necessary ... . For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with normal saline during transport ... . Do not use emetics. For ingestion, rinse mouth and administer 5 ml/kg up to 200 ml of water for dilution if the patient can swallow, has a strong gag reflex, and does not drool ... . Cover skin burns with dry sterile dressings after decontamination ... . /Poison A and B/[Bronstein, A.C., P.L. Currance; Emergency Care for Hazardous Materials Exposure. 2nd ed. St. Louis, MO. Mosby Lifeline. 1994., p. 139] **PEER REVIEWED**

Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary edema, or is in respiratory arrest. Positive pressure ventilation techniques with a bag valve mask device may be beneficial. Monitor cardiac rhythm and treat arrhythmias as necessary ... . Start an IV with D5W /SRP: "To keep open", minimal flow rate/. Use lactated Ringer's if signs of hypovolemia are present. Watch for signs of fluid overload. Consider drug therapy for pulmonary edema ... . For hypotension with signs of hypovolemia, administer fluid cautiously. Watch for signs of fluid overload ... . Treat seizures with diazepam (Valium) ... . Use proparacaine hydrochloride to assist eye irrigation ... . /Poison A and B/[Bronstein, A.C., P.L. Currance; Emergency Care for Hazardous Materials Exposure. 2nd ed. St. Louis, MO. Mosby Lifeline. 1994., p. 139] **PEER REVIEWED**

ANIMAL TOXICITY STUDIES:

EVIDENCE FOR CARCINOGENICITY:

Cancer Classification: Group D Not Classifiable as to Human Carcinogenicity[USEPA Office of Pesticide Programs, Health Effects Division, Science Information Management Branch: "Chemicals Evaluated for Carcinogenic Potential" (April 2006)] **QC REVIEWED**

CLASSIFICATION: D; not classifiable as to human carcinogenicity. BASIS FOR CLASSIFICATION: In animals local sarcomas have been induced after implantation of foils and disks of silver. However, the interpretation of these findings has been questioned due to the phenomenon of solid-state

carcinogenesis in which even insoluble solids such as plastic have been shown to result in local fibrosarcomas. ANIMAL CARCINOGENICITY DATA: Inadequate .[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS). Summary on Silver (7440-22-4). Available from, as of March 15, 2000: http://www.epa.gov/iris/] **PEER REVIEWED**

NON-HUMAN TOXICITY EXCERPTS:

Silver metal in the rabbit eye anterior chamber causes little reaction, and in the vitreous body induces no clinically evident inflammation, but atrophic changes in the retina have been found by microscopic exam. In the cornea, silver particles become ensheathed in a connective tissue coating, and the surface is discolored by gray-white material assumed to be silver chloride, and also by black material assumed to be silver sulfide.[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 817] **PEER REVIEWED**

SILVER FOIL WAS FOUND TO BE HIGHLY TOXIC WHEN IMPLANTED IN BRAIN TISSUES OF ANIMALS WHILE SC IMPLANTATION OF THIN SILVER FOIL INDUCES FIBROSARCOMAS IN RATS.[Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 36] **PEER REVIEWED**

Silver, either as silver metal or silver chloride, exerted toxic effects on the smooth muscle of isolated cannulated hamster cheek pouch arterioles. Silver initially stimulated the smooth muscle, producing a marked vasoconstriction. The vessels then dilated back to control diameters. Once the arterioles began to dilate, they became refractory to norepinephrine or potassium stimulation.[Jackson Wf, Duling BR; Circ Res 53 (1): 105-8 (1983)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/6861293?dopt=Abstract" target=new>PubMed Abstract

Percutaneous silver wire implants were looped through the dorsal skin of rats and inoculated with Staphylococcus aureus to test the effect on bacteria in the tract. ... No giant cells or toxicity were seen.[Spadaro JA et al; J Biomed Matter Res 20 (5): 565-77 (1986)] **PEER REVIEWED**

Repeated exposure of animals to silver may produce anemia, cardiac enlargement, growth retardation, and degenerative changes in the liver.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 622] **PEER REVIEWED**

The ultrastructural localization of silver deposits was noted in the eye of rats exposed to silver either perorally or intraperitoneally. Silver was found in lysosomes of most cell types, an exception being the neural retina. Extracellularly, silver was present in vascular basal laminae an in connection with connective tissue fibers. Systemic silver intoxication was found to result in a rapid and long lasting deposition of the metal in the eye.[Rungby J; Exp Mol Pathol 45 (1): 22-30 (1986)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3758305?dopt=Abstract" target=new>PubMed Abstract

Macrophages were obtained by washing the peritoneum of four unstimulated adult male NMRI-mice with isotonic buffered saline. Upon settling of

cells, four cultures derived from each mouse were exposed to 80 or 20 micromolar silver lactate, 80 micromolar sodium lactate, or control medium. Macrophages exposed to either concentration of silver lactate exhibited reduced survival as compared to controls. Cells exposed to the highest silver concentration granulated and fragmented while still attached to the culture substrate. Cells exposed to the lower silver concentration released from the substrate. Silver grains were observed by microscopy in all silver treated cells, invariably located in lysosome like dense bodies. In addition, significant enhancement of malondialdehyde production was observed in liver tissue derived from mice administered silver lactate by the intraperitoneal route. No significant difference in hepatic malondialdehyde production was observed in animals treated for 3 days or with a single silver lactate injection.[Rungby J et al; Arch Toxicol 59 (6): 408-12 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3606385?dopt=Abstract" target=new>PubMed Abstract

A simple, rapid assay, based on the lysosomal incorporation of neutral red by cells, conveniently carried out in 96 well microtiter plates, was used to evaluate the cytotoxic effect of cationic and anionic metal salts on BALB/c mouse 3T3 fibroblasts. Ranking of the metals according to their decreasing potency was based on spectrophotometrically determined absorbance of the neutral red, extracted from surviving viable cells. The rank order was cadmium > mercury > silver > zinc > manganese > copper > cobalt > nickel > chromium (III) for the cationic metals. Cationic metals incubated with cultures in medium containing 1% fetal bovine serum were 3-4 times more toxic than in medium with 10% fetal bovine serum.[Borenfreud E, Puerner JA; Toxicol 39 (2): 121-34 (1986)] **PEER REVIEWED**

Exposure of Nostoc muscorum to different concentrations of nickel and silver brought about reduction in growth, carbon fixation, heterocyst production, and nitrogenase activity and increase in the loss of ions (K+, Na+). In an attempt to ameliorate the toxicity of test metals by ascorbic acid, glutathione, and sulfur containing amino acids (L-cysteine and L-methionine), it was found that the level of protection by ascorbic acid and glutathione was more for Ag than nickel. However, metal induced inhibition of growth and carbon fixation was equally ameliorated by methionine. But the level of protection by cysteine was quite different, ie, 27% for nickel and 22% for Ag.[Rai LC, Raizada M; Ecotox Environ Safety 14 (1): 12-21 (1987)] **PEER REVIEWED**

In a rat carcinogenicity study designed to avoid solid state carcinogenesis, a suspension of silver powder in trioctanion was given once a month by intramuscular (i.m.) injection to Fischer 344 rats (50/sex/group). The dose given was 5 mg each for 5 treatments and 10 mg each for 5 more treatments, for a total of 75 mg of silver. ... No fibrosarcomas (0/50) appeared at the injection site in silver treated animals. Injection site sarcoma were found only in the vehicle control (1/50) ... . The latent period in the vehicle control group was 19 months, ... The authors concluded that finely divided silver powder injected i.m. did not induce cancer ... .[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.10 Sept 1992. Available from, as of Feb 24, 2002:

http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

In a carcinogenicity study in rats, colloidal silver (dose unspecified) injected subcutaneously resulted in tumors in 8 of 26 rats surviving more than 14 months. In 6/8 rats, the tumor was at the subcutaneous injection site. In 700 untreated rats, the rate of spontaneous tumor formation was 1 to 3%; no vehicle control was reported ... .[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.10 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

Adult crayfish (Cambarus diogenes diogenes) exposed to 8.41 +/- 0.17 microg silver/L (19.4% as Ag+) in moderately hard freshwater under flow-through conditions for 96 h exhibited ionoregulatory disturbance, elevated metabolic ammonia (T(amm)) production and substantial silver accumulation in the gills, hemolymph, and hepatopancreas. The ionoregulatory disturbance included both a generally reduced unidirectional Na+ influx and an increased unidirectional Na+ efflux, leading to a substantial net loss of Na+ from the silver-exposed crayfish. The Na+ uptake in silver-exposed crayfish differed overall from controls, while the increased Na+ efflux recovered to control values 48 hr into the 96 h of exposure. The general inhibition of Na+ uptake could be explained by a reduced sodium/potassium-adenosine triphosphatase (Na/K-ATPase) activity in terminally obtained gill samples from the silver-exposed crayfish. The silver-induced effect on Na+ uptake and loss translated to reduced hemolymph Na+ concentrations but not significantly reduced hemolymph Cl- concentrations. Hemolymph T(anim) and T(amm) efflux both increased in silver-exposed crayfish, indicating an increased metabolic T(amm) production. The present study demonstrates that the toxic mechanism of waterborne silver exposure in freshwater crayfish resembles that of freshwater teleost fish. The crayfish might therefore be a useful model system for extending current environmental regulatory strategies, currently based on teleost fish, to invertebrates.[Grosell M et al; Environ Toxicol Chem 21 (2): 369-74 (2002)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11833807?dopt=Abstract" target=new>PubMed Abstract

Silver metal in the rabbit anterior chamber causes little reaction, and in the vitreous body induces no clinically evident inflammation, but atrophic changes in the retina have been found by microscopic exam. In the cornea, silver particles become ensheathed in a connective tissue coating, and the surface is discolored by gray-white material assumed to be silver chloride, and also by black material assumed to be silver sulfide.[Grant, W.M. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas Publisher, 1986., p. 817] **PEER REVIEWED**

NON-HUMAN TOXICITY VALUES:

LD50 Rat (male) oral > 5000 mg/kg[USEPA; Reregistration Eligibility Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

LD50 Rat (male) dermal > 2000 mg/kg[USEPA; Reregistration Eligibility

Decision Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

METABOLISM/ PHARMACOKINETICS:

ABSORPTION, DISTRIBUTION & EXCRETION:

Excretion of silver from the body is mainly gastrointestinal. Urinary excretion (around 10 ug/day) and fecal elimination (30-80 ug/day) has been reported from two healthy subjects. ... These values might reflect a certain overestimation of true silver concn. ... Using neutron activation analysis ... 1 ug/day /was found/ in urine of normal persons.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 621] **PEER REVIEWED**

The deposition fraction of 0.5 um spherical silver particles in the lung of dogs has been found to be about 17%. ... The intestinal absorption of silver by mice, rats, monkeys, and dogs has been recorded at about 10% or less following ingestion of radioactive silver.[Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 524] **PEER REVIEWED**

Absorption upon exposure or the extent of exposure, itself, may vary considerably among normals as reflected in tissue levels. For example, the silver content of the hair of school children from 21 school districts in Selesia, Poland, ranged from 0.23 to 1.96 mg/kg (average 0.69 mg/kg; analyses by neutron activation).[Dutkuwicz T et al; Chem Anal 23: 261 (1978) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-1 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Distribution of silver in the rat at day 6 following intramuscular injections of 1.0 mg dose of silver; 53.5 percent of the dose was absorbed (0.59 percent absorbed by the heart and lung; 2.69 percent absorbed by spleen; 3.03 percent absorbed by blood; 33.73 percent absorbed by liver; 0.63 percent absorbed by kidney; 8.21 percent absorbed by GI tract; 2.39 percent absorbed by muscle; 2.20 percent absorbed by bone; 7.39 percent absorbed by skin; 1.82 percent excreted by urine; 37.33 percent absorbed by feces) and 46.5 percent of absorbed by the heart and lung; 0.01 percent absorbed by spleen; 0.50 percent absorbed by blood; 0.36 percent absorbed by liver; 0.07 percent absorbed by kidney; 1.12 percent absorbed by GI tract; 0.27 percent absorbed by muscle; 0.18 percent absorbed by bone; 0.24 percent absorbed by skin; 0.64 percent excreted by urine; 96.56 percent excreted in feces) and 7.9 percent was unabsorbed.[Scott KG, Hamilton JG; J Clin Invest 27: 555 (1948) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-47 (1980) EPA 440/5-80-071] **PEER REVIEWED**

... /An/ elimination pattern was detected in rats after iv administration of silver ... . Most of the radioactivity found in the feces was eliminated via the bile ... .[USEPA; Reregistration Eligibility Decision

Document - Silver. Washington, DC: USEPA, Off Pest Prog. USEPA 738-R-94-021, p.12 Sept 1992. Available from, as of Feb 24, 2002: http://www.epa.gov/pesticides/reregistration/status.htm] **PEER REVIEWED**

A study in dogs indicates that absorption of inhaled metallic silver particles with a median aerodynamic diameter of approximately 0.5 um is extensive, and is not dependent upon particle size ... . Absorption was measured in one dog that remained anesthetized during the entire period between exposure and sacrifice. In this dog, 3.1% (0.8 ug) of the deposited material was dissolved, transported out of the lungs, and was found mostly in liver and blood 6 hr after exposure; a 1 ug/cm2/day absorption rate for metallic silver was est by the authors. Up to 90% of the deposited silver was est to be absorbed into the systemic circulation based on all experimental data.[DHHS/ATSDR; Toxicological Profile for Silver p. 24 TP-90-24 (1990)] **PEER REVIEWED**

Using whole-body spectrometer measurements obtained from a person accidently exposed to radiolabeled silver, ... estimated that 25% of the detectable (110 m)Ag was distributed to the liver between 2 and 6 days after exposure.[DHHS/ATSDR; Toxicological Profile for Silver p. 27 TP-90-24 (1990)] **PEER REVIEWED**

... reported that 96.9%, 2.4%, and 0.35% of the dose /of metallic silver/ initially deposited in the lungs of a dog following intratracheal admin was detected in the lungs, liver and blood, respectively, 6 hr after exposure. The remaining silver was detected in the gall bladder and bile (0.14%), intestines (0.10%), kidneys (0.06%), and stomach (0.02%). The distribution of metallic silver (expressed as a percentage of the initial amt deposited) 225 days after exposure differed from that at 6 hr, with the majority of the metal detected in the liver (0.49%), brain (0.035%), gall bladder and bile (0.034%), intestines (0.028%), lungs and trachea (0.019%), bone (0.014%), stomach and contents (0.012%), heart (0.009%), and muscle (0.007%). The distribution to tissues other than the lungs is similar at 6 hr and 225 days if silver in the lungs is not considered. At both time points the majority of the silver is found in the liver (approx 77% of the total body silver excluding lung content).[DHHS/ATSDR; Toxicological Profile for Silver p. 27 TP-90-24 (1990)] **PEER REVIEWED**

In rats, silver was unevenly distributed in organs and tissues following iv or im injection of radiolabeled metallic silver and/or silver nitrate, respectively. The highest concn were found, in decr order, in the GI tract, liver, blood, kidney, muscle, bone, and skin following im injection ... . Following iv injection the highest concn were found, in decr order, in the liver, pancreas, spleen, and plasma ... . the proportion of the dose distributed to the tissues is positively correlated with the dose admin ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 28 TP-90-24 (1990)] **PEER REVIEWED**

The clearance of radioactive silver metal dust in a man who was accidentally exposed illustrated the rapid removal of silver from the lungs primarily by ciliary action, with subsequent ingestion and ultimate elimination in the feces ... . Lung clearance fit a biexponential profile ... . Radioactive silver was detected in the feces up to 300 days after exposure, but was not detected in urine samples (collected up to 54 days

after exposure).[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-90-24 (1990)] **PEER REVIEWED**

In dogs, lung clearance of metallic silver particles (avg aerodynamic diameter of 0.5 um) following intra-tracheal intubation was accompanied by an incr in silver conc in the area of the stomach and liver. The incr in silver concn in the stomach suggests that some proportion of the silver particles are cleared by the mucociliary escalator and swallowed. However, the predominant route of clearance from the lung appeared to be through dissolution of the silver and transport through the blood. The silver was apparently carried by the blood to the liver, with little cleared via the mucociliary passages ... . Approx 90% of the inhaled dose was excreted in the feces within 30 days of exposure.[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-90-24 (1990)] **PEER REVIEWED**

Silver removal from the liver by biliary excretion was demonstrated ... . Control rats and rats with ligated bile ducts were admin radioactive metallic silver by im injection. In rats with ligated bile ducts, excretion of silver in the feces was 19%, compared to 97% in controls. Deposition in the liver of rats with ligated bile ducts was 48% and 2.5% in the GI tract compared to 0.36 and 1.12%, respectively in the controls ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**

... determined that biliary excretion accounted for between 24% and 45% of the silver admin to rats. The concn of silver in the bile was est to be between 16 and 20 times greater than that in plasma. An incr in the bile/liver tissue ratio (ug/ml per ug/g) from 4.2 to 6.4 indicates that more silver is concentrated in the bile as the dose of silver incr. It is believed that active transport is involved in the transfer of silver from the plasma to the bile ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**

Rats excreted silver in the bile at 10 times the rate of rabbits. Dogs excreted silver in the bile at a rate lower than that of rabbits ... . Dogs had the highest amt of silver retained in the liver (2.9 ug silver/g), as compared to the rabbit (2.13 ug silver/g) and rat (1.24 ug silver/g).[DHHS/ATSDR; Toxicological Profile for Silver p. 32 TP-90-24 (1990)] **PEER REVIEWED**

Silver, once deposited in the body, is poorly excreted in the urine in amounts detectable by spectrochemical methods. /Silver metal and soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**

IF DUST OF METAL OR ITS SALTS IS ABSORBED, IT IS PRECIPITATED IN TISSUES IN METALLIC STATE & CANNOT BE ELIMINATED FROM BODY IN THIS STATE. /SILVER & CMPD/[International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983., p. 2047] **PEER REVIEWED**

Silver is absorbed after topical application, ingestion, or inhalation. GI

uptake ranges from < 1% of the admin dose in rats, mice, & monkeys to as much as 10% in dogs. Following intratracheal admin of 0.5 um metallic silver particles, 97% of the dose remained in dog lung at 6 hr after treatment; the rate of systemic absorption was calculated as 1 ug/sq cm/day. Of the absorbed silver, 77% of the dose was found in dog liver at 225 days after admin. Pulmonary clearance was triphasic with half-times of 1.7, 8.4, & 40 days. Parenteral injection of metallic silver or silver nitrate demonstrated that rat, dog, & rabbit liver & gut retained the highest silver concns. Silver was eliminated primarily in the bile. /Silver and compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**

Fecal elimination by rats, dogs, & monkeys accounts for up to 99% of the ingested silver. /Silver and compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**

Takenaka S et al; Environ Health Perspect 109 Suppl 4: 547-51 (2001)] The cardiovascular system is currently considered a target for particulate matter, especially for ultrafine particles. In addition to autonomic or cytokine mediated effects, the direct interaction of inhaled materials with the target tissue must be examined to understand the underlying mechanisms. In the first approach, pulmonary and systemic distribution of inhaled ultrafine elemental silver (EAg) particles was investigated on the basis of morphology and inductively coupled plasma mass spectrometry (ICP-MS) analysis. Rats were exposed for 6 hr at a concentration of 133 microg EAg m(3) (3 x 10(6) cm(3), 15 nm modal diameter) and were sacrificed on days 0, 1, 4, and 7. ICP-MS analysis showed that 1.7 microg Ag was found in the lungs immediately after the end of exposure. Amounts of Ag in the lungs decreased rapidly with time, and by day 7 only 4% of the initial burden remained. In the blood, significant amounts of Ag were detected on day 0 and thereafter decreased rapidly. In the liver, kidney, spleen, brain, and heart, low concentrations of Ag were observed. Nasal cavities, especially the posterior portion, and lung-associated lymph nodes showed relatively high concentrations of Ag. For comparison, rats received by intratracheal instillation either 150 microL aqueous solution of 7 microg silver nitrate (AgNO(3) (4.4 microg Ag) or 150 microL aqueous suspension of 50 microg agglomerated ultrafine EAg particles. A portion of the agglomerates remained undissolved in the alveolar macrophages and in the septum for at least 7 days. In contrast, rapid clearance of instilled water-soluble AgNO(3) from the lung was observed. These findings show that although instilled agglomerates of ultrafine EAg particles were retained in the lung, Ag was rapidly cleared from the lung after inhalation of ultrafine EAg particles, as well as after instillation of AgNO(3), and entered systemic pathways. **PEER REVIEWED**

Regardless of route and chemical form administered, fecal excretions of silver always predominate over urinary excretion. Most absorbed silver is excreted into the intestine by the liver via the bile. /Silver/[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-56 (1980) EPA 440/5-80-071] **PEER REVIEWED**

The deposition fraction of 0.5 um spherical silver-particles in the lung of dogs has been found to be about 17%. ... The intestinal absorption of silver by mice, rats, monkeys, & dogs has been recorded at about 10% or less following ingestion of radioactive silver. /Silver/[Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 524] **PEER REVIEWED**

Silver was found only as a lipoid-silver complex or in lipofuschin-like lysosomes & in residual bodies. The lysosomes were thought to be responsible for the intracellular transport & extrusion of silver. In the liver, there was incr activity of cytochrome oxidase, but marked decr in the activity of succinate dehydrogenase. /Silver/[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-49 (1980) EPA 440/5-80-071] **PEER REVIEWED**

BIOLOGICAL HALF-LIFE:

The biological half-life for silver is a few days for animals and up to 50 days for human liver.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 621] **PEER REVIEWED**

After rabbits had inhaled 4 um monodispersed silver coated Teflon particles, /it was/ found that an avg of 30% of the particles deposited were cleared from the lung in one day and another 30% during the rest of the first week of the exposure. After exposure by inhalation, dogs cleared 59% of an admin dose of radioactive silver from the lungs in 1.7 days. The liver had a somewhat slower clearance of 9 days. An apparent biological half-time of about 1 day was found by whole-body scintillation counting in mice, rats, monkeys, and dogs after oral ingestion. ... Somewhat longer half-times were observed for these species after iv injection of silver, with monkeys and dogs having half-times of 1.8 and 2.4 days, respectively.[Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 525] **PEER REVIEWED**

High local concn of silver from a prosthetic cement were associated with a slowly resolving focal neuropathy. The terminal elimination half-life in this 78 year old patient was long (approx 6 months).[Ellenhorn, M.J. and D.G. Barceloux. Medical Toxicology - Diagnosis and Treatment of Human Poisoning. New York, NY: Elsevier Science Publishing Co., Inc. 1988., p. 1060] **PEER REVIEWED**

In rats, silver is eliminated from the lung in two or three phases. The fastest phase (0.3 to 1.7 days) removes most of the inhaled dose by mucociliary clearance. A second phase and third phase remove absorbed silver, mostly via the liver, with half-lives of about 8 to 15 and 40 to 50 days, respectively.[USEPA; Ambient Water Quality Criteria Doc: Silver p.C-58 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Clearance of deposited silver particles from the lung /of a dog/ fit a triexponential profile, with biological half-lives of 1.7, 8.4, and 40

days, accounting for 59, 39, and 2% of the radioactivity excreted, respectively. Clearance of absorbed silver from the liver fit a biexponential profile with biological half-lives of 9.0 and 40 days accounting for 97% and 3% of the radioactivity excreted, respectively ... .[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-24-90 (1990)] **PEER REVIEWED**

/Human/... Lung clearance fit a biexponential profile, with biological half-lives of 1 and 52 days.[DHHS/ATSDR; Toxicological Profile for Silver p. 30 TP-90-24 (1990)] **PEER REVIEWED**

MECHANISM OF ACTION:

Light catalyzes the reduction of silver salts deposited in skin to metallic silver & it /is/ subsequently oxidized to silver sulfide; it is the deposition of the latter compound which accounts for the gray discoloration pathognomonic of argyria. /Silver and compounds/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1397] **PEER REVIEWED**

INTERACTIONS:

The binding of Ag+ to metallothionein was investigated, and a silver saturation assay was developed for the measurement of metallothionein in tissues. When samples of purified hepatic zinc metallothionein or cadmium metallothionein were titrated with Ag+ followed by RBC hemolysate-heat treatment (to remove non-MT bound Ag+), it was found that saturation of MT occurred at 17 to 18 g-atoms Ag+/mol protein. The rank order of potencies of metals to displace Ag+ from 110mAg-labelled Ag-metallothionein was Ag+ > Cu2+ > Cd(2+) > Hg(2+) > Zn(2+) at pH 8.5 in 0.5 M glycine buffer. ...[Scheuhammer AM, Cherian MG; Toxicol Appl Pharmacol 82 (3): 417-25 (1986)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3952727?dopt=Abstract" target=new>PubMed Abstract

The antagonism between silver and selenium is mediated through the selenium containing enzyme glutathione perioxidase. To test the effect of selenium intake on silver toxicity, two levels of silver, 76 and 751 mg/l, and a control (no silver) were administered in drinking water for 52 days. All experimental groups consisted of ten, 21 day old Holtzman rats, fed a vitamin E deficient diet. A similar regimen was administered to vitamin E deficient rats which had selenium added to their diet. Silver, at 751 mg/l severely depressed the growth of rats on the low selenium diet. Selenium addition overcame this deficit completely in the 76 mg/l silver group but not in the 751 mg/l group. Activity of liver glutathione perioxidase in the selenium supplemented group was reduced to 30% of control at 76 mg/l silver in drinking water and to 4 % of control at 751 mg/l. This activity was not reduced at all in erthrocytes and was not detectable in the livers of rats fed the low selenium (0.02 ppm) basal diets.[Wagner PA et al; Proc Soc Exp Biol Med 148: 1106-10 (1975) USEPA, Office of Drinking Water; Criteria Document (Draft): Silver p.V-8 (1985)] **PEER REVIEWED**

Experiments to clarify the relationship between ceruloplasmin synthesis and copper (Cu) status involving metallothionein induction as modified by

cadmium (Cd), silver (Ag), and lead (Pb) were described. Specific pathogen free male mice, age 5 weeks, were fed /ad libitin/ a standard diet containing 11 ppm Cu. Metals were injected subcutaneously three times every 24 hours at doses of 1.5 mg/kg Ag, 20 mg/kg Pb, 1.5 mg/kg Cd, and 3.0 mg/kg Cu. Two groups were treated with combinations of Cd plus Ag and Cu plus Ag, the metals being injected at the same time but at different sites. Mice were sacrificed at 24 hours postinjection and serum was collected to determine ceruloplasmin activity and metal content. Liver homogenates and bile were also assessed. Cd injection significantly increased serum ceruloplasmin and serum Cu, accompanied by an increase in hepatic Cu. Pb injection slightly increased serum ceruloplasmin and serum Cu. Ag injection significantly reduced ceruloplasmin activity and Cu levels in serum and slightly increased hepatic Cu. The Ag effect was evident in combination with Cd. Cu in combination with Ag negated the effect of Ag on ceruloplasmin with a concomitant loss of Ag from serum ceruloplasmin.[Sugawara N, Sugawara C; Arch Toxicol 59 (6): 432-6 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3606389?dopt=Abstract" target=new>PubMed Abstract

Intraperitoneal pretreatment with a large dose of cadmium, zinc, mercury, manganese or silver remarkably depressed the lethal effects of X-ray. Metal binding protein may not play an important role in protective effects of metal pretreatment on the lethal effects of X-ray, but quantum mechanical characters of metals may do so.[Nomiyama K et al; Sangyo Ika Daigaku Zasshi 9: 95-110 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3602751?dopt=Abstract" target=new>PubMed Abstract

PHARMACOLOGY:

INTERACTIONS:

The binding of Ag+ to metallothionein was investigated, and a silver saturation assay was developed for the measurement of metallothionein in tissues. When samples of purified hepatic zinc metallothionein or cadmium metallothionein were titrated with Ag+ followed by RBC hemolysate-heat treatment (to remove non-MT bound Ag+), it was found that saturation of MT occurred at 17 to 18 g-atoms Ag+/mol protein. The rank order of potencies of metals to displace Ag+ from 110mAg-labelled Ag-metallothionein was Ag+ > Cu2+ > Cd(2+) > Hg(2+) > Zn(2+) at pH 8.5 in 0.5 M glycine buffer. ...[Scheuhammer AM, Cherian MG; Toxicol Appl Pharmacol 82 (3): 417-25 (1986)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3952727?dopt=Abstract" target=new>PubMed Abstract

The antagonism between silver and selenium is mediated through the selenium containing enzyme glutathione perioxidase. To test the effect of selenium intake on silver toxicity, two levels of silver, 76 and 751 mg/l, and a control (no silver) were administered in drinking water for 52 days. All experimental groups consisted of ten, 21 day old Holtzman rats, fed a vitamin E deficient diet. A similar regimen was administered to vitamin E deficient rats which had selenium added to their diet. Silver, at 751 mg/l

severely depressed the growth of rats on the low selenium diet. Selenium addition overcame this deficit completely in the 76 mg/l silver group but not in the 751 mg/l group. Activity of liver glutathione perioxidase in the selenium supplemented group was reduced to 30% of control at 76 mg/l silver in drinking water and to 4 % of control at 751 mg/l. This activity was not reduced at all in erthrocytes and was not detectable in the livers of rats fed the low selenium (0.02 ppm) basal diets.[Wagner PA et al; Proc Soc Exp Biol Med 148: 1106-10 (1975) USEPA, Office of Drinking Water; Criteria Document (Draft): Silver p.V-8 (1985)] **PEER REVIEWED**

Experiments to clarify the relationship between ceruloplasmin synthesis and copper (Cu) status involving metallothionein induction as modified by cadmium (Cd), silver (Ag), and lead (Pb) were described. Specific pathogen free male mice, age 5 weeks, were fed /ad libitin/ a standard diet containing 11 ppm Cu. Metals were injected subcutaneously three times every 24 hours at doses of 1.5 mg/kg Ag, 20 mg/kg Pb, 1.5 mg/kg Cd, and 3.0 mg/kg Cu. Two groups were treated with combinations of Cd plus Ag and Cu plus Ag, the metals being injected at the same time but at different sites. Mice were sacrificed at 24 hours postinjection and serum was collected to determine ceruloplasmin activity and metal content. Liver homogenates and bile were also assessed. Cd injection significantly increased serum ceruloplasmin and serum Cu, accompanied by an increase in hepatic Cu. Pb injection slightly increased serum ceruloplasmin and serum Cu. Ag injection significantly reduced ceruloplasmin activity and Cu levels in serum and slightly increased hepatic Cu. The Ag effect was evident in combination with Cd. Cu in combination with Ag negated the effect of Ag on ceruloplasmin with a concomitant loss of Ag from serum ceruloplasmin.[Sugawara N, Sugawara C; Arch Toxicol 59 (6): 432-6 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3606389?dopt=Abstract" target=new>PubMed Abstract

Intraperitoneal pretreatment with a large dose of cadmium, zinc, mercury, manganese or silver remarkably depressed the lethal effects of X-ray. Metal binding protein may not play an important role in protective effects of metal pretreatment on the lethal effects of X-ray, but quantum mechanical characters of metals may do so.[Nomiyama K et al; Sangyo Ika Daigaku Zasshi 9: 95-110 (1987)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/3602751?dopt=Abstract" target=new>PubMed Abstract

ENVIRONMENTAL FATE & EXPOSURE:

PROBABLE ROUTES OF HUMAN EXPOSURE:

Silver may be released from silver amalgam dental fillings when placed in unlined cavities ...[Leirskar J; Scand J Dent Res 82: 74 (1974) as cited in USEPA; Ambient Water Quality Criteria Doc: Silver p.C-21 (1980) EPA 440/5-80-071] **PEER REVIEWED**

Where men work with metallic silver, small particles may accidentally penetrate the exposed skin. ... This may occur in occupations involving the filing, drilling, hammering, turning, engraving, polishing, forging,

soldering & smelting of silver.[International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983., p. 2047] **PEER REVIEWED**

METALLIC SILVER MAY BE INHALED BY SILVER FINISHERS LEADING TO ABNORMAL CHEST X-RAY FINDINGS.[Hamilton, A., and H. L. Hardy. Industrial Toxicology. 3rd ed. Acton, Mass.: Publishing Sciences Group, Inc., 1974., p. 171] **PEER REVIEWED**

BODY BURDEN:

Urine samples collected from six males, aged 28 to 51 years, who had been employed in jewelry handicraft for 7 to 23 years, were analyzed for silver. Urinary silver ranged from 5 to 261 micrograms per 24 hours. A mean value of about 27 micrograms was found after shifts over 5 days in workers performing investment casting with oxyacetylene flame, while the mean urinary silver level in workers performing the electromagnetic induction process was about 5 micrograms after shifts.[Minoia C et al; Occupational and Environmental Chemical Hazards p.349-54 (1987)] **PEER REVIEWED**

NATURAL POLLUTION SOURCES:

... found native or associated with copper, gold, and lead.[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

FISH/SEAFOOD CONCENTRATIONS:

Metal concentrations were measured in selected fish and invertebrate species from Mugu Lagoon, Malibu Lagoon and Ballona Wetlands in southern California in order to assess the extent of metal contamination in these three wetlands. Ranges of element concentrations (in microgram/g) found in biota were: Zn 12-650; Cu 1.9-440; Ni < 1-37; Cr < 1-55; Pb < 0.5-6.8; As < 1-8.5; Se < 1-3.8; Cd < 0.2-0.90; and Ag < 0.3-5.9. Relative to previous studies of California biota, the highest metal concentrations found were for chromium and nickel. The highest levels were in one of the two bottom-dwelling fish (juvenile Leptocottus armatus) (55 ug/g) and the two water-column fish sampled (Fundulus parvipinnis and Atherinops affinis) (30 and 24 ug/g). At Ballona Lagoon, elevated levels of copper and silver were found in the bivalve Tagelus californianus (440 and 5.9 ug/g). Chromium and nickel appeared to be most persistent in fish from Mugu (4.6-55 and 2.6-37 ug/g), the most northern site and an active military base, and Ballona (< 1-30 and < 1-16 ug/g), believed to be the most metal-contaminated site. Compared to previously measured metal concentrations in species of California coastal waters, these regions revealed higher levels of chromium, nickel, silver, arsenic, zinc, copper and, to a lesser extent, cadmium and selenium. Chromium and silver were present at high enough levels at all three sites to be considered environmental health hazards.[Cohen T et al; Mar Pollut Bull 42 (3): 224-32 (2001)] **PEER REVIEWED** <a href="http://www.ncbi.nlm.nih.gov/pubmed/11381877?dopt=Abstract" target=new>PubMed Abstract

ENVIRONMENTAL STANDARDS & REGULATIONS:

FIFRA REQUIREMENTS:

As the federal pesticide law FIFRA directs, EPA is conducting a comprehensive review of older pesticides to consider their health and environmental effects and make decisions about their future use. Under this pesticide reregistration program, EPA examines health and safety data for pesticide active ingredients initially registered before November 1, 1984, and determines whether they are eligible for reregistration. In addition, all pesticides must meet the new safety standard of the Food Quality Protection Act of 1996. Pesticides for which EPA had not issued Registration Standards prior to the effective date of FIFRA '88 were divided into three lists based upon their potential for human exposure and other factors, with List B containing pesticides of greater concern and List D pesticides of less concern. Silver and Cmpds is found on List D. Case No: 4082; Pesticide type: fungicide, herbicide, antimicrobial; Case Status: RED Approved 06/93; OPP has made a decision that some/all uses of the pesticide are eligible for reregistration, as reflected in a Reregistration Eligibility Decision (RED) document.; Active ingredient (AI): silver; Data Call-in (DCI) Date(s): 9/30/92; AI Status: OPP has completed a Reregistration Eligibility Decision (RED) for the case/AI.[USEPA/OPP; Status of Pesticides in Registration, Reregistration and Special Review p.335 (Spring, 1998) EPA 738-R-98-002] **PEER REVIEWED**

RCRA REQUIREMENTS:

D011; A solid waste containing silver may or may not become characterized as a hazardous waste when subjected to the Toxicity Characteristic Leaching Procedure listed in 40 CFR 261.24, and if so characterized, must be managed as a hazardous waste. /Silver/[40 CFR 261.24 (7/1/2001)] **PEER REVIEWED**

CLEAN WATER ACT REQUIREMENTS:

Toxic pollutant designated pursuant to section 307(a)(1) of the Federal Water Pollution Control Act and is subject to effluent limitations. /Silver and compounds/[40 CFR 401.15 (7/1/2001)] **QC REVIEWED**

The ambient water quality criterion for silver is recommended to be identical to the existing water standard which is 50 ug/l. /Silver and cmpd/[USEPA; Ambient Water Quality Criteria Doc: Silver p.vi (1980) EPA 440/5-80-071] **QC REVIEWED**

FEDERAL DRINKING WATER GUIDELINES:

EPA 100 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

STATE DRINKING WATER STANDARDS:

(CT) CONNECTICUT 50 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

STATE DRINKING WATER GUIDELINES:

(AZ) ARIZONA 50 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

(ME) MAINE 35 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

(MN) MINNESOTA 30 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

(WI) WISCONSIN 50 ug/l[USEPA/Office of Water; Federal-State Toxicology and Risk Analysis Committee (FSTRAC). Summary of State and Federal Drinking Water Standards and Guidelines (11/93) To Present] **QC REVIEWED**

FDA REQUIREMENTS:

[21 CFR 73.2500 (4/1/2000)] Certification of this color additive when used for coloring fingernail polish at a level not to exceed 1 percent of the final product is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification pursuant to section 721(c) of the act.[21 CFR 73.2500 (4/1/2001)] **PEER REVIEWED**

CHEMICAL/PHYSICAL PROPERTIES:

MOLECULAR FORMULA:

Ag **PEER REVIEWED**

MOLECULAR WEIGHT:

107.86[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

COLOR/FORM:

White metal, face-centered cubic structure[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

Metal: White lustrous solid.[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

BOILING POINT:

Approx 2000 deg C[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ:

Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

MELTING POINT:
960.5 deg C[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

CORROSIVITY:
Sol silver cmpd will attack some forms of plastics, rubber, and coatings. /Silver metal and soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**

DENSITY/SPECIFIC GRAVITY:
10.49 @ 15 deg C[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

SOLUBILITIES:
Sol in fused alkali hydroxides in presence of air, fused peroxides, and alkali cyanides in presence of oxygen[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

INSOL IN HOT OR COLD WATER, ALKALI; SOL IN NITRIC ACID; HOT SULFURIC ACID, POTASSIUM CYANIDE /Aqueous/[Weast, R.C. (ed.) Handbook of Chemistry and Physics, 68th ed. Boca Raton, Florida: CRC Press Inc., 1987-1988., p. B-127] **PEER REVIEWED**

OTHER CHEMICAL/PHYSICAL PROPERTIES:
Poor reflector of UV[Weast, R.C. (ed.) Handbook of Chemistry and Physics, 68th ed. Boca Raton, Florida: CRC Press Inc., 1987-1988., p. B-35] **PEER REVIEWED**

Pure silver has highest electrical & thermal conductivity and lowest contact resistance of all metals.[Lide, DR (ed.). CRC Handbook of Chemistry and Physics. 81st Edition. CRC Press LLC, Boca Raton: FL 2000, p. 4-28] **PEER REVIEWED**

MOLTEN METAL DISSOLVES 20 TIMES ITS VOL OF OXYGEN UNDER 1 ATM & GIVES IT UP ON SOLIDIFICATION.[Browning, E. Toxicity of Industrial Metals. 2nd ed. New York: Appleton-Century-Crofts, 1969., p. 296] **PEER REVIEWED**

Soft, ductile, malleable, lustrous white metal.[Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 10th ed. Volumes 1-3 New York, NY: John Wiley & Sons Inc., 1999., p. V3 3211] **PEER REVIEWED**

Silver has the oxidation states +1, and less frequently +2; higher ones are rare.[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988.,

p. 620] **PEER REVIEWED**

CHEMICAL SAFETY & HANDLING:

HAZARDS SUMMARY:

The major hazards encountered in the use and handling of silver stem from its toxicologic properties. Toxic by all routes (ie, inhalation, ingestion, and dermal contact), exposure to silver (as a finely divided metal, or in solution) may occur from its use in electroplating, as a component of photographic materials, in the manufacture of jewelry, mirrors, coinage, pigments, antiseptics, and in brazing and welding. Effects from exposure may include skin or eye irritation, mild bronchitis, metal fume fever, and argyria, a blue-gray discoloration of the skin, mucous membranes, and eyes. Also, hepatic damage has been implicated with soluble silver salts. The OSHA PEL is set at a TWA of 0.01 mg/cu m. Safe levels should be maintained by the use of engineering controls (eg, local exhaust ventilation, or process enclosure). In activities where over-exposure to silver may occur, workers should wear impervious clothing, gloves, face protection, and a self-contained breathing apparatus. Such clothing and equipment should be removed before leaving the worksite. Skin that becomes contaminated with silver should be promptly washed. Eating and smoking should be prohibited in silver work areas. Finely divided silver dust is flammable. Also, explosive compounds may form when silver mixes with acetylene, ammonia, or hydrogen peroxide. Before shipping silver, consult with the regulatory requirements of the US Department of Transportation. If powdered silver or solutions of silver are spilled, first ventilate the area, then collect the spilled material (solutions are first absorbed in vermiculite, dry sand, or earth) and place in sealed containers for reclamation. Before implementing land disposal of silver waste, consult with environmental regulatory agencies for guidance. **PEER REVIEWED**

FIRE POTENTIAL:

NONCOMBUSTIBLE, EXCEPT AS POWDER[Sax, N.I. and R.J. Lewis, Sr. (eds.). Hawley's Condensed Chemical Dictionary. 11th ed. New York: Van Nostrand Reinhold Co., 1987., p. 1042] **PEER REVIEWED**

The dust is flammable[ITII. Toxic and Hazarous Industrial Chemicals Safety Manual. Tokyo, Japan: The International Technical Information Institute, 1982., p. 464] **PEER REVIEWED**

HAZARDOUS REACTIVITIES & INCOMPATIBILITIES:

SILVER IS ... INCOMPATIBLE WITH OXALIC ACID & TARTARIC ACID.[Fire Protection Guide to Hazardous Materials. 12 ed. Quincy, MA: National Fire Protection Association, 1997., p. 491-169] **PEER REVIEWED**

INERT TO MOST ACIDS; READILY REACTS WITH DIL NITRIC ACID, HOT CONCENTRATED SULFURIC ACID.[The Merck Index. 10th ed. Rahway, New Jersey: Merck Co., Inc., 1983., p. 1221] **PEER REVIEWED**

/In the reaction of silver & acetylene/ an insoluble, explosive acetylide is formed. The reaction between ammonia & gold, silver, or

mercury produces fulminate-like compounds of variable & uncertain composition that explode when dried. Bromoazide explodes on contact with ... silver foil. When silver is treated with nitric acid in presence of ethyl alcohol, silver fulminate may be formed, which can be detonated. Ethyleneimine forms explosive compounds with silver. ... Finely divided silver & strong hydrogen peroxide soln may explode.[Fire Protection Guide to Hazardous Materials. 12 ed. Quincy, MA: National Fire Protection Association, 1997., p. 491-169] **PEER REVIEWED**

Incompatible with ... acetylene compounds; aziridine; 3-bromopropyne; caroxylic acids; copper + ethylene glycol; electrolytes + zinc; ethylene oxide; ethyl hydroperoxide; iodoform; ozonides; peroxomonosulfuric acid; peroxyformic acid.[Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 2929] **PEER REVIEWED**

Contact of metallic silver and sol silver cmpd with acetylene may cause formation of silver acetylide that is sensitive to shock. Contact with ammonia may cause formation of cmpd that are explosive when dry. Contact with strong hydrogen peroxide solutions will cause violent decomp to oxygen gas. /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**

Acetylene, ammonia, hydrogen peroxide, bromoazide, chlorine, trifluoride, ethyleneimine, oxalic acid, tartaric acid. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

HAZARDOUS DECOMPOSITION:

Toxic gases and vapors (such as oxides of nitrogen) may be released when some sol silver cmpd decomp. /Silver metal and soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**

IMMEDIATELY DANGEROUS TO LIFE OR HEALTH:

10 mg/cu m (as ag). /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

PROTECTIVE EQUIPMENT & CLOTHING:

Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent skin contact with powdered metallic silver or solids or liquids containing sol silver cmpd, where skin contact may occur. /Silver metal & sol silver cmpd/[Mackison, F.

W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 3] **PEER REVIEWED**

Employees should be provided with and required to use dust- and splash-proof safety goggles where there is any possibility of powdered metallic silver or solids or liquids containing soluble silver compounds contacting the eyes. /Silver metal and soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 3] **PEER REVIEWED**

Wear appropriate personal protective clothing to prevent skin contact. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Wear appropriate eye protection to prevent eye contact. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Respirator Recommendations: Up to 0.25 mg/m cu: (APF = 25) Any supplied-air respirator operated in a continuous-flow mode. Substance causes eye irritation or damage; eye protection needed./(Air Protetion Factor = 25) Any powered, air-purifying respirator with a high-efficiency particulate filter. Substance causes eye irritation or damage; eye protection needed. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Eyewash fountains should be provided in areas where there is any possibility that workers could be exposed to the substance; this is irrespective of the recommendation involving the wearing of eye protection. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Respirator Recommendations: Up to 0.5 mg/cu m: (APF = 50) Any air-purifying, full-facepiece respirator with a high-efficiency particulate filter/(APF = 50) Any self-contained breathing apparatus with a full facepiece/(APF = 50) Any supplied-air respirator with a full facepiece. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of

Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Respirator Recommendations: Up to 10 mg/m3: (APF = 2000) Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode Emergency or planned entry into unknown concentrations or IDLH conditions: (APF = 10,000) Any self-contained breathing apparatus that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode/(APF = 10,000) Any supplied-air respirator that has a full facepiece and is operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained positive-pressure breathing apparatus. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Respirator Recommendations: Escape: (APF = 50) Any air-purifying, full-facepiece respirator with a high-efficiency particulate filter/Any appropriate escape-type, self-contained breathing apparatus. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

PREVENTIVE MEASURES:

SRP: The scientific literature for the use of contact lenses in industry is conflicting. The benefit or detrimental effects of wearing contact lenses depend not only upon the substance, but also on factors including the form of the substance, characteristics and duration of the exposure, the uses of other eye protection equipment, and the hygiene of the lenses. However, there may be individual substances whose irritating or corrosive properties are such that the wearing of contact lenses would be harmful to the eye. In those specific cases, contact lenses should not be worn. In any event, the usual eye protection equipment should be worn even when contact lenses are in place. **PEER REVIEWED**

If employees' clothing may have become contaminated with solids or liquids containing sol silver cmpd, employees should change into uncontaminated clothing before leaving the work premises. Clothing contaminated with metallic silver or silver compounds should be placed in closed containers for storage until it can be discarded or until provision is made for the removal of substances from the clothing. If the clothing is to be laundered or otherwise cleaned to remove the substances, the person performing the operation should be informed of substances' hazardous properties. Non-impervious clothing which becomes contaminated with metallic silver or sol silver cmpd should be removed promptly and not reworn until the metallic silver or sol silver cmpd are removed from the clothing. /Silver metal or soluble silver compounds/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123

(3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 3] **PEER REVIEWED**

Skin that becomes contaminated with metallic silver or sol silver cmpd should be promptly washed or showered to remove any metallic silver or sol silver cmpd. Eating and smoking should not be permitted in areas where metallic silver or solids or liquids or liquids containing sol silver cmpd are handled, processed, or stored. Employees who handle powdered metallic silver should wash their hands thoroughly before eating, smoking, or using toilet facilities. /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 3] **PEER REVIEWED**

... Control methods which may be effective ... /include/ local exhaust ventillation, general dilution ventilation, personal protective equipment & process enclosure. /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 3] **PEER REVIEWED**

The worker should immediately wash the skin when it becomes contaminated. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

Work clothing that becomes wet or significantly contaminated should be removed and replaced. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

STABILITY/SHELF LIFE:

STABLE IN ... AIR & WATER; TARNISHES WHEN EXPOSED TO OZONE, HYDROGEN SULFIDE OR AIR CONTAINING SULFUR.[Weast, R.C. (ed.) Handbook of Chemistry and Physics, 68th ed. Boca Raton, Florida: CRC Press Inc., 1987-1988., p. B-35] **PEER REVIEWED**

Heat /contributes to instability/ /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 2] **PEER REVIEWED**

CLEANUP METHODS:

If powdered silver metal or sol silver cmpd are spilled or leaked, the following steps should be taken: 1. Ventilate area of spill or leak. 2. Collect spilled material in most convenient & safe manner & deposit in sealed containers for reclamation. Liquid containing silver

metal or sol silver cmpd should be absorbed in vermiculite, dry sand, earth, or similar material. /Silver metal & sol silver cmpd/[Mackison, F. W., R. S. Stricoff, and L. J. Partridge, Jr. (eds.). NIOSH/OSHA - Occupational Health Guidelines for Chemical Hazards. DHHS(NIOSH) Publication No. 81-123 (3 VOLS). Washington, DC: U.S. Government Printing Office, Jan. 1981., p. 4] **PEER REVIEWED**

DISPOSAL METHODS:

SRP: At the time of review, criteria for land treatment or burial (sanitary landfill) disposal practices are subject to significant revision. Prior to implementing land disposal of waste residue (including waste sludge), consult with environmental regulatory agencies for guidance on acceptable disposal practices. **PEER REVIEWED**

OCCUPATIONAL EXPOSURE STANDARDS:

OSHA STANDARDS:

Permissible Exposure Limit: Table Z-1 8-hr Time Weighted Avg: 0.01 mg/cu m. /Silver, metal and compounds (as Ag)/[29 CFR 1910.1000 (7/1/2001)] **PEER REVIEWED**

THRESHOLD LIMIT VALUES:

8 Hr Time Weighted Average (TWA): 0.1 mg/cu m.[American Conference of Governmental Industrial Hygienists TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH, 2008, p. 52] **QC REVIEWED**

Excursion Limit Recommendation: Excursions in worker exposure levels may exceed 3 times the TLV-TWA for no more than a total of 30 minutes during a work day, and under no circumstances should they exceed 5 times the TLV-TWA, provided that the TLV-TWA is not exceeded.[American Conference of Governmental Industrial Hygienists TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH, 2008, p. 52] **QC REVIEWED**

NIOSH RECOMMENDATIONS:

Recommended Exposre Limit: 10 Hr Time-Weighted Avg: 0.01 mg/cu m. /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

IMMEDIATELY DANGEROUS TO LIFE OR HEALTH:

10 mg/cu m (as ag). /Silver (metal dust and soluble compounds, as Ag)/[NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. U.S. Department of Health & Human Services, Public Health Service, Center for Disease Control & Prevention. DHHS (NIOSH) Publication No. 2001-145 (CD-ROM) August 2001.] **PEER REVIEWED**

OTHER STANDARDS REGULATIONS AND GUIDELINES:

Other nations: Australia: metal 0.1 mg/cu m, soluble compounds as Ag, 0.01

mg/cu m; Federal Republic of Germany: metal 0.01 mg/cu m total dust, short-term level 0.1 mg/cu m, 30 min, once/shift; United Kingdom: metal 0.1 mg/cu m (guidance limit to be reviewed), compounds as Ag 0.01 mg/cu m. /Silver & cmpd/[American Conference of Governmental Industrial Hygienists, Inc. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Volumes I, II, III. Cincinnati, OH: ACGIH, 1991., p. 1398] **PEER REVIEWED**

MANUFACTURING/USE INFORMATION:

USES:

For Silver (USEPA/OPP Pesticide Code: 072501) ACTIVE products with label matches. /SRP: Registered for use in the U.S. but approved pesticide uses may change periodically and so federal, state and local authorities must be consulted for currently approved uses./[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Silver (7440-22-4). Available from, as of February 26, 2002: http://npirspublic.ceris.purdue.edu/ppis/] **PEER REVIEWED**

For coinage, most frequently alloyed with copper or gold; for manuf tableware, mirrors, jewelry, ornaments; for electroplating; for making vessels and apparatus used in manuf medicinal chemicals, in processing foods and beverages, in handling organic acids; as catalyst in hydrogenation and oxidation processes; as ingredient of dental alloys.[O'Neil, M.J. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., 2001., p. 1525] **PEER REVIEWED**

Brazes and solders, coinage, jewelry, tableware, photography, photochromic glass, electrical contacts, silver thick films, electroplating, electroless plating, magnetron sputtered reflective coatings, dental amalgam, bearings in jet engines, giant magnetoresistance.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 176] **PEER REVIEWED**

Electrical contacts; high capacity silver-zinc & silver-cadmium batteries[Seiler, H.G., H. Sigel and A. Sigel (eds.). Handbook on the Toxicity of Inorganic Compounds. New York, NY: Marcel Dekker, Inc. 1988., p. 620] **PEER REVIEWED**

BEARING LININGS IN AIR-COOLED AIRCRAFT ENGINES[Venugopal, B. and T.D. Luckey. Metal Toxicity in Mammals, 2. New York: Plenum Press, 1978., p. 32] **PEER REVIEWED**

MEDICATION **PEER REVIEWED**

MANUFACTURERS:

The Sunshine Mine and Refining Co.; Production site: Kellogg, ID. /Closed operations Feb 16, 2001/[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

Echo Bay Mines Ltd; Production site: McCoy/Cove Gold-Silver Mine (location not provided)[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

Hecla Mining Co.; Production site: Lucky Friday Mine, northern Idaho[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

Kennecott Greens/Kennecott Juneau/Hecla Mining Co joint venture; Production site: Greens Creek Mine, Admiralty Island National Monument, Alaska.[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

Coeur d'Alene Mines Corp; Production site: Galena Mine, Wallace, ID.[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

METHODS OF MANUFACTURING:

Silver is ... recovered during electrolytic refining of copper.[Lide, DR (ed.). CRC Handbook of Chemistry and Physics. 81st Edition. CRC Press LLC, Boca Raton: FL 2000, p. 4-28] **PEER REVIEWED**

Cyanide process: Cyanide solution is mixed with zinc dust to precipitate the silver.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 170] **PEER REVIEWED**

Chlorination process: roasted ore with chlorides followed by a hot brine leach and subsequent precipitation of the silver on copper.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 170] **PEER REVIEWED**

Mercury method: Ores are ground with mercury, salt, copper sulfate, and sulfuric acid, and then steam heated to recover silver.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 170] **PEER REVIEWED**

Aqua regia method: Extraction of silver from ores using aqua-regia[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 170] **PEER REVIEWED**

Heap leaching method: spraying of sodium cyanide solution over roughly crushed ores heaped on an imperious pad has become the most economical way or recovering precious metals (e.g., silver) from very low grade

ores.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 171] **PEER REVIEWED**

Activated carbon method: Passing of cyanide solution over activated carbon to adsorb the precious metals, which are then stripped from the charcoal by a hot caustic solution. Electrowinning removes the precious metals from this solution, depositing them on the cathode.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 170] **PEER REVIEWED**

FORMULATIONS/PREPARATIONS:

USEPA/OPP Pesticide Code 072501; Trade Names:Argentum, L-3, Shell Silver.[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Silver (7440-22-4). Available from, as of February 26, 2002: http://npirspublic.ceris.purdue.edu/ppis/] **PEER REVIEWED**

Forms avail: pure (fine), sterling (7.5% copper), various alloys, plate; ingot, bullion, moss, sheet, wire, tubing, castings; powder; high purity (impurities less than 100 ppm); single crystals; whiskers.[Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997., p. 999] **PEER REVIEWED**

Available: 99.99 wt% Ag & 99.90 wt% Ag[Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984., p. 21(83) 10] **PEER REVIEWED**

Amalgum-70% silver, 26% tin, 3% copper, and 1% zinc is used in combination with mercury to fill cavities in teeth.[CONSIDINE. CHEMICAL AND PROCESS TECHNOL ENCYC 1974 p.1038] **PEER REVIEWED**

Alloys: Ag-Au; Ag-Cu; Ag-Pd; Ag-Pt; Ag-Cu-Ni; Ag-Mg-Ni; Ag-Au-Cd-Cu; & Ag-Cd-Cu-Ni[CONSIDINE. CHEMICAL AND PROCESS TECHNOL ENCYC 1974 p.1037] **PEER REVIEWED**

ASTM B413 grade (Grade 99.90 Refined): 99.90 wt% Ag; MIL-S-13282b (Grade A): 99.95 wt% Ag; SAE/UNS P07931 (sterling silver): 92.10-93.50 wt% Ag[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 173] **PEER REVIEWED**

IMPURITIES:

ASTM B413 grade (Grade 99.90 Refined): 0.002 wt% Fe, 0.025 wt% Pb, 0.001 wt% Bi, 0.08 wt% Cu; MIL-S-13282b (Grade A): 0.005 wt% Fe, 0.025 wt% Pb, 0.001 wt% Bi, 0.10 wt% Cu, 0.001 wt% Se, 0.001 wt% Te; SAE/UNS P07931 (sterling silver): 0.05 wt% Fe, 0.03 wt% Pb, 0.05 wt% Ca, 0.06 wt% Zn, all others 0.06 wt%.[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 173] **PEER REVIEWED**

CONSUMPTION PATTERNS:

PHOTOGRAPHIC MATERIALS, 43%; ELECTRIC & ELECTRONIC PRODUCTS, 26%; STERLING WARE, 6%; BRAZING ALLOYS & SOLDERS, 6%; ELECTROPLATED WARE,

2%; CATALYSTS, 2%; COMMEMORATIVE MEDALS, 2%; MINTED COINAGE, 2%; OTHER, 11% (1982)[SRI] **PEER REVIEWED**

Photography, 45%; electrical and electronics products, 25%; sterlingware, electroplated ware, and jewelry, 11%; brazing alloys and solders, 5%; other, 14% (1986)[BUREAU OF MINES. MINERAL COMMODITY SUMMARIES 1987 p.144] **PEER REVIEWED**

In 2000, U.S. consumption of silver, including scrap, was estimated to have been about 5,600 tons. Photography, the largest end-use category, accounted for about 2,990 tons. The second largest end-use category, batteries/electrical/electronic products, consumed about 1,060 tons. About 500 tons of silver was consumed in sterlingware, jewelry, and silverplate. Global consumption was estimated to have ben 25,000 tons, and increase of more than 435 tons from that consumed in 1999.[USGS; Minerals Yearbook: Volume I.-- Metals and Minerals Database on Silver. Available from, as of March 8th, 2002: http://minerals.usgs.gov/minerals/pubs/commodity/silver/880400.pdf] **PEER REVIEWED**

U. S. PRODUCTION:
(1978) 3.79X10+9 G[SRI] **PEER REVIEWED**

(1982) 3.39X10+9 G[SRI] **PEER REVIEWED**

(1986) 2.61X10+9 g[BUREAU OF MINES. MINERAL COMMODITY SUMMARIES 1987 p.144] **PEER REVIEWED**

U. S. IMPORTS:
(1978) 2.36X10+9 G[SRI] **PEER REVIEWED**

(1982) 3.64X10+9 G[SRI] **PEER REVIEWED**

(1986) 4.23X10+9 g[BUREAU OF MINES. MINERAL COMMODITY SUMMARIES 1987 p.144] **PEER REVIEWED**

(2001) 140,052 kg[USDC; Trade and Economy: Data and Analysis. Silver (7440-22-4) US Dept. Commerce. International Trade Admin. Available from, as of March 8, 2002: http://www.ita.doc.gov/td/industry/otea/] **PEER REVIEWED**

U. S. EXPORTS:
(1978) 6.84X10+8 G[SRI] **PEER REVIEWED**

(1982) 7.78X10+8 G[SRI] **PEER REVIEWED**

(1986) 8.71X10+8 g[BUREAU OF MINES. MINERAL COMMODITY SUMMARIES 1987 p.144] **PEER REVIEWED**

(2001) 63,592 kg[USDC; Trade and Economy: Data and Analysis. Silver (7440-22-4) US Dept. Commerce. International Trade Admin. Available from, as of March 8, 2002: http://www.ita.doc.gov/td/industry/otea/] **PEER REVIEWED**

LABORATORY METHODS:

SPECIAL REFERENCES:

SYNONYMS AND IDENTIFIERS:

SYNONYMS:

L 3 **PEER REVIEWED**

V 9 **PEER REVIEWED**

Algaedyn **PEER REVIEWED**

Amalgum **PEER REVIEWED**

ARGENTUM **PEER REVIEWED**

Caswell No 735 **PEER REVIEWED**

C I 77820 **PEER REVIEWED**

USEPA/OPP Pesticide Code: 072501.[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Silver (7440-22-4). Available from, as of February 26, 2002: http://npirspublic.ceris.purdue.edu/ppis/] **PEER REVIEWED**

EPA pesticide chemical code 072501 **PEER REVIEWED**

Germany: C-Pigment 2 **PEER REVIEWED**

Shell silver[Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 2929] **PEER REVIEWED**

SILBER (GERMAN) **PEER REVIEWED**

SILFLAKE 135 **PEER REVIEWED**

Silpowder 130 **PEER REVIEWED**

SILVER ATOM **PEER REVIEWED**

Silver, colloidal **PEER REVIEWED**

SILVER METAL **PEER REVIEWED**

SR 999 **PEER REVIEWED**

TCG 7R **PEER REVIEWED**

FORMULATIONS/PREPARATIONS:

USEPA/OPP Pesticide Code 072501; Trade Names:Argentum, L-3, Shell Silver.[U.S. Environmental Protection Agency/Office of Pesticide Program's Chemical Ingredients Database on Silver (7440-22-4). Available from, as of February 26, 2002: http://npirspublic.ceris.purdue.edu/ppis/] **PEER REVIEWED**

Forms avail: pure (fine), sterling (7.5% copper), various alloys, plate; ingot, bullion, moss, sheet, wire, tubing, castings; powder; high purity (impurities less than 100 ppm); single crystals; whiskers.[Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. 1997., p. 999] **PEER REVIEWED**

Available: 99.99 wt% Ag & 99.90 wt% Ag[Kirk-Othmer Encyclopedia of Chemical Technology. 3rd ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984., p. 21(83) 10] **PEER REVIEWED**

Amalgum-70% silver, 26% tin, 3% copper, and 1% zinc is used in combination with mercury to fill cavities in teeth.[CONSIDINE. CHEMICAL AND PROCESS TECHNOL ENCYC 1974 p.1038] **PEER REVIEWED**

Alloys: Ag-Au; Ag-Cu; Ag-Pd; Ag-Pt; Ag-Cu-Ni; Ag-Mg-Ni; Ag-Au-Cd-Cu; & Ag-Cd-Cu-Ni[CONSIDINE. CHEMICAL AND PROCESS TECHNOL ENCYC 1974 p.1037] **PEER REVIEWED**

ASTM B413 grade (Grade 99.90 Refined): 99.90 wt% Ag; MIL-S-13282b (Grade A): 99.95 wt% Ag; SAE/UNS P07931 (sterling silver): 92.10-93.50 wt% Ag[Kirk-Othmer Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present., p. V22 (1997) 173] **PEER REVIEWED**

EPA HAZARDOUS WASTE NUMBER:

D011; A waste containing silver may or may not be characterized as a hazardous waste following testing by the Toxicity Characteristic Leaching Procedure as prescribed by the Resource Conservation and Recovery Act (RCRA) regulations. /Silver/

ADMINISTRATIVE INFORMATION:

HAZARDOUS SUBSTANCES DATABANK NUMBER: 5034

LAST REVISION DATE: 20050623

LAST REVIEW DATE: Reviewed by SRP on 5/11/2002

UPDATE HISTORY:

Field Update on 2010-09-07, 1 fields added/edited/deleted

Field Update on 2010-04-27, 1 fields added/edited/deleted

Field Update on 2009-04-16, 2 fields added/edited/deleted

Field Update on 2008-08-15, 25 fields added/edited/deleted

Field Update on 2007-06-07, 1 fields added/edited/deleted

Complete Update on 2005-06-23, 1 fields added/edited/deleted

Field Update on 2005-04-29, 4 fields added/edited/deleted

Field Update on 2005-01-29, 2 fields added/edited/deleted

Complete Update on 02/14/2003, 1 field added/edited/deleted.

Complete Update on 08/29/2002, 69 fields added/edited/deleted.

Field Update on 08/06/2002, 1 field added/edited/deleted.

Complete Update on 01/18/2002, 2 fields added/edited/deleted.

Field Update on 01/14/2002, 1 field added/edited/deleted.

Complete Update on 08/09/2001, 1 field added/edited/deleted.

Complete Update on 03/30/2000, 1 field added/edited/deleted.

Complete Update on 02/09/2000, 1 field added/edited/deleted.

Complete Update on 02/02/2000, 1 field added/edited/deleted.

Complete Update on 09/21/1999, 1 field added/edited/deleted.

Complete Update on 08/30/1999, 8 fields added/edited/deleted.

Field Update on 08/26/1999, 1 field added/edited/deleted.

Complete Update on 05/04/1999, 1 field added/edited/deleted.

Complete Update on 04/08/1999, 1 field added/edited/deleted.

Complete Update on 03/31/1999, 2 fields added/edited/deleted.

Complete Update on 01/29/1999, 1 field added/edited/deleted.

Complete Update on 11/24/1998, 1 field added/edited/deleted.

Complete Update on 11/19/1998, 2 fields added/edited/deleted.

Complete Update on 11/17/1998, 1 field added/edited/deleted.

Complete Update on 06/02/1998, 1 field added/edited/deleted.

Complete Update on 11/01/1997, 1 field added/edited/deleted.

Complete Update on 09/08/1997, 1 field added/edited/deleted.

Complete Update on 08/13/1997, 1 field added/edited/deleted.

Complete Update on 04/24/1997, 1 field added/edited/deleted.

Complete Update on 03/18/1997, 1 field added/edited/deleted.

Complete Update on 02/28/1997, 1 field added/edited/deleted.

Complete Update on 04/30/1996, 2 fields added/edited/deleted.

Complete Update on 04/09/1996, 7 fields added/edited/deleted.

Field Update on 01/28/1996, 1 field added/edited/deleted.

Complete Update on 01/24/1995, 1 field added/edited/deleted.

Complete Update on 01/09/1995, 1 field added/edited/deleted.

Complete Update on 11/18/1994, 1 field added/edited/deleted.

Complete Update on 08/04/1994, 1 field added/edited/deleted.

Complete Update on 03/25/1994, 1 field added/edited/deleted.

Complete Update on 08/07/1993, 1 field added/edited/deleted.

Field update on 01/03/1993, 1 field added/edited/deleted.

Complete Update on 01/28/1992, 1 field added/edited/deleted.

Complete Update on 07/09/1991, 2 fields added/edited/deleted.

Complete Update on 05/08/1991, 1 field added/edited/deleted.

Field update on 11/09/1990, 1 field added/edited/deleted.

Field update on 12/29/1989, 1 field added/edited/deleted.

Complete Update on 12/19/1989, 1 field added/edited/deleted.

Complete Update on 07/12/1989, 72 fields added/edited/deleted.

Field Update on 02/10/1989, 1 field added/edited/deleted.

Complete Update on 03/05/1988, 73 fields added/edited/deleted.

Complete Update on 03/31/1986

Created 19830315 by GCF

TOXICOLOGICAL PROFILE FOR SILVER

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

December 1990

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law (also known as SARA) directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The list of the 200 most significant hazardous substances was published in the Federal Register on April 17, 1987 and on October 20, 1988.

Section 110 (3) of SARA directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiologic evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects,

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure which present a significant risk to human health of acute, subacute, and chronic health effects, and

(C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature that describes a hazardous substance's toxicological properties. Other literature is presented but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the statement is material that presents levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the front of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available; therefore, we encourage comment that will make the toxicological profile series of the greatest use.

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, EPA, the Centers for Disease Control, and the National Toxicology Program. It has also been reviewed by a panel of nongovernment peer reviewers and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances
and Disease Registry

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about silver and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1177 sites on its National Priorities List (NPL). Silver has been found at 27 of these sites. However, we do not know how many of the 1177 NPL sites have been evaluated for silver. As EPA evaluates more sites, the number of sites at which silver is found may change. The information is important for you because silver may cause harmful health effects and because these sites are potential or actual sources of human exposure to silver.

When a chemical is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with it.

If you are exposed to a hazardous substance such as silver, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your. individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS SILVER?

Silver is one of the basic elements that make up our planet. Silver is rare, but occurs naturally in the environment as a soft, "silver" colored metal. Because silver is an element, there are no man-made sources of silver. People make jewelry, silverware, electronic equipment, and dental fillings with silver in its metallic form. It also occurs in powdery white (silver nitrate and silver chloride) or dark-gray to black compounds (silver sulfide and silver oxide). Silver could be found at hazardous waste sites in the form of these compounds mixed with soil and/or water. Therefore, these silver compounds will be the main topic of this profile. Throughout the profile the various silver compounds will at times be referred to simply as silver.

Photographers use silver compounds to make photographs. Photographic materials are the major source of the silver that is released into the environment. Another source is mines that produce silver and other metals.

1. PUBLIC HEALTH STATEMENT

The natural wearing down of silver-bearing rocks and soil by the wind and rain also releases large amounts of silver into the environment.

Silver that is released into the environment may be carried long distances in air and water. Rain washes silver compounds out of many soils so that it eventually moves into the groundwater. Silver is stable and remains in the environment in one form or another until it is taken out again by people. Because silver is an element, it does not break down, but it can change its form by combining with other substances. Over time it may change from the form first released, to metallic silver, and then back to the same or other compounds. The form it is found in depends on environmental conditions. More information on the chemical and physical properties of silver compounds can be found in Chapter 3, on its production, use, and disposal in Chapter 4, and on silver in the environment in Chapters 4 and 5.

1.2 HOW MIGHT I BE EXPOSED TO SILVER?

Most people are exposed daily to very low levels of silver mainly in food and drinking water, and less in air. The silver in these sources is at least partially due to naturally occurring silver in water and soil. Skin contact and breathing in air containing silver compounds also occurs in the workplace. Other sources of exposure include the use of silver in medicines, and in activities such as jewelry-making, soldering, and photography. Exposure from everyday use, such as wearing jewelry or eating with silver-coated flatware, is not expected to result in silver being taken into the body.

Silver levels of less than 0.000001 mg silver per cubic meter of air (mg/m^3), 0.2-2.0 parts silver per billion parts water (ppb) in surface waters, such as lakes and rivers, and 0.20-0.30 parts silver per million parts soil (ppm) in soils are found from naturally occurring sources. Silver compounds are also found in groundwater and at hazardous waste sites throughout the United States. Drinking water supplies in the United States have been found to contain silver levels of up to 80 ppb. Surveys show that one-tenth to one-third of samples taken from drinking water supplies (both groundwater and surface water) contain silver at levels greater than 30 ppb. For more information on exposure to silver see Chapter 5.

1.3 HOW CAN SILVER ENTER AND LEAVE MY BODY?

Silver may enter your body through the mouth, throat, or digestive tract after eating food or drinking water that contains silver, or through your lungs after breathing air containing silver. It can also enter your body through your skin when you put your hands into solutions containing silver compounds, such as those used in photography, or when you come in contact with silver-containing powders. Silver is also known to enter the body when medicines containing it are taken or applied to the skin or gums. Generally, much less silver will enter the body through the skin than through the lungs or stomach.

Because many silver compounds dissolve in water and do not evaporate, the most common way that silver may enter the body of a person near a hazardous waste site is by drinking water that contains silver or eating food grown near the site in soil that contains silver. Silver can also enter the body when soil that has silver in it is eaten. Most of the silver that is eaten or breathed in leaves the body in the feces within about a week. Very little passes through the urine. It is not known how much of the silver that enters the body through the skin leaves the body. Some of the silver that is eaten, inhaled, or passes through the skin may build up in many places in the body. More information on how silver enters and leaves the body can be found in Chapter 2.

1.4 HOW CAN SILVER AFFECT MY HEALTH?

Since at least the early part of this century, doctors have known that silver compounds can cause some areas of the skin and other body tissues to turn gray or blue-gray. Doctors call this condition "argyria." Argyria occurs in people who eat or breathe in silver compounds over a long period (several months to many years). A single exposure to a silver compound may also cause silver to be deposited in the skin and in other parts of the body; however, this is not known to be harmful. It is likely that many exposures to silver are necessary to develop argyria. Once you have argyria it is permanent. However, the condition is thought to be only a "cosmetic" problem. Most doctors and scientists believe that the discoloration of the skin seen in argyria is the most serious health effect of silver.

Exposure to dust containing relatively high levels of silver compounds such as silver nitrate or silver oxide may cause breathing problems, lung and throat irritation and stomach pain. These effects have been seen in workers in chemical manufacturing facilities that make silver nitrate and silver oxide. One man developed severe breathing problems shortly after working with molten silver. Skin contact with silver compounds has been found to cause mild allergic reactions, such as rash, swelling, and inflammation, in some people.

Studies of the health effects of silver in animals commonly use silver nitrate. Doctors and scientists assume that effects seen using silver nitrate in animals will be very similar to effects in humans caused by any silver compound. While this is likely to be true, it is still possible that some silver compounds will be more harmful, or toxic, than silver nitrate.

One animal study suggests that long-term exposure (125 days) to moderately high levels of silver nitrate in drinking water may have a slight effect on the brain because exposed animals were less active than animals drinking water without silver. Another study found that some of the animals that drank water containing moderately high levels of silver for most of their lives (9 months or longer) had hearts that were larger than normal. It is not yet known whether these effects would occur in humans. There have been

suggestions in some occupational studies in humans that silver can cause kidney problems; however, more people exposed to silver need to be studied to find out if silver causes these effects.

No studies of cancer or birth defects in animals from eating, drinking, or breathing in silver compounds were found. Therefore, it is not known if these effects would occur in humans. One study of animals drinking silver compounds mixed with water for most of their life found no effect on fertility. Another study found that reproductive tissues were damaged in animals after they received injections of silver nitrate. However, the tissues recovered even while the animals received more injections of silver nitrate. Tests in animals show that silver compounds are likely to be life-threatening for humans only when large amounts (that is, grams) are swallower and that skin contact with silver compounds is very unlikely to be lifethreatening.

Silver does have helpful uses. For example, silver nitrate was used for many years as drops in newborns' eyes to prevent blindness caused by gonorrhea, and is also used in salves for burn victims. Some water treatment methods (including water filters) also use a form of silver to kill bacteria. More information on the health effects from exposure to silver is presented in Chapter 2. More information on the helpful uses of silver is presented in Chapter 4.

1.5 WHAT LEVELS OF EXPOSURE HAVE RESULTED IN HARMFUL HEALTH EFFECTS?

Reports of cases of argyria suggest that gram amounts of a silver compound taken in medication in small doses over several months may cause argyria in some humans. People who work in factories that manufacture silver compounds can also breathe in the compounds. In the past, some of these workers have become argyric. However, the level of silver in the air and the length of exposure that caused argyria in these workers is not known. It is also not known what level of silver causes breathing problems, lung and throat irritation, or stomach pain in people.

Studies in rats show that drinking water containing very large amounts of silver (2589 parts of silver per million parts of water, or about 2.6 grams per liter) is likely to be life-threatening.

There is very little information about health effects following skin contact with silver compounds. Argyria that covers the entire body is not seen following skin contact with silver compounds, although the skin may change color where it touches the silver. However, many people who have used skin creams containing silver compounds such as silver nitrate and silver sulphadiazine have not reported health problems from the silver in the medicine. In one animal study, a strong solution of silver nitrate (about 41 grams of silver nitrate per liter of water which is equal to 41 parts of

silver nitrate per thousand parts of water) applied to the skin of guinea pigs for 28 days did not cause the animals to die; however, it did cause the guinea pigs to stop gaining weight normally. It is not known if this would happen to people if they were exposed the same way.

Tables l-1 through l-4 present the information that is available concerning specific levels of exposure and health effects. The amount of silver that has caused death in rats, and that has caused mice to be less active are shown in Table 1-4.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SILVER?

There are reliable and accurate ways of measuring silver in the body. Silver can be measured in the blood, urine, feces, and body tissues of exposed individuals. Because urine and blood samples are easy to get, these fluids are most often used to find out if a person has been exposed to silver in the last week or so. Silver builds up in the body, and the best way to learn if past exposure has occurred is to look for silver in samples of skin. Tests for silver are not commonly done at a doctor's office because they require special equipment. Although doctors can find out if a person has been exposed to silver by having blood or skin samples examined, they can not tell whether any health effects will occur. Information about tests for measuring silver in the body is in Chapters 2' and 6.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed regulations and guidelines to protect people from the possible health effects from long-term exposure to silver in drinking water. The Environmental Protection Agency (EPA) suggests that the level of silver in drinking water not be more than 0.05 milligrams per liter of water (mg/L) (which is equal to 50 parts of silver per billion parts of water or ppb). However, in May, 1989, the EPA announced that this restriction on silver levels in drinking water might be removed. For shortterm exposures (l-10 days), EPA suggests that drinking water levels of silver not be more than 1.142 mg/L (which is equal to 1.142 parts of silver per million parts of water or ppm).

Any release to the environment of more than 1 pound silver nitrate or 1000 pounds of silver alone should be reported to the National Response Center. To limit the amount silver workers are exposed to during an 8-hour shift for a 40-hour work week, the Occupational Safety and Health Administration (OSHA) has set a legal limit (Permissible Exposure Limit or PEL) of 0.01 milligrams of silver per cubic meter of air (mg/m^3) in workroom air.

TABLE 1-1. Human Health Effects from Breathing Silver*

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to air containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to air containing specific levels of silver are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-2. Animal Health Effects from Breathing Silver

Short-term Exposure (less than or equal to 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of animals to air containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Air	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of animals to air containing specific levels of silver are not known.

TABLE 1-3. Human Health Effects from Eating or Drinking Silver*

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from short-term exposure of humans to food containing specific levels of silver are not known.
Levels in Water		The health effects resulting from short-term exposure of humans to water containing specific levels of silver are not known.
Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects
		The health effects resulting from long-term exposure of humans to food containing specific levels of silver are not known.
Levels in Water		The health effects resulting from long-term exposure of humans to water containing specific levels of silver are not known.

*See Section 1.2 for a discussion of exposures encountered in daily life.

TABLE 1-4. Animal Health Effects from Eating or Drinking Silver

Short-term Exposure (less than or equal to 14 days)		
Levels in Food	Length of Exposure	Description of Effects*
		The health effects resulting from short-term exposure of animals to food containing specific levels of silver are not known.
Levels in Water (ppm)		
2589	2 weeks	Death in rats.

Long-term Exposure (greater than 14 days)		
Levels in Food	Length of Exposure	Description of Effects*
		The health effects resulting from long-term exposure of animals to food containing specific levels of silver are not known.
Levels in Water (ppm)		
95	125 days	Sluggish behavior in mice.
1587	37 weeks	Decreased weight gain in rats.

*These effects are listed at the level at which they were first observed. They may also be seen at higher levels.

For more information on criteria and standards for silver exposure, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your State Health or Environmental Department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also give you information on the location of the nearest occupational and environmental health clinics. Such clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

This chapter contains descriptions and evaluations of studies and interpretation of data on the health effects associated with exposure to silver. Its purpose is to present levels of significant exposure for silver based on toxicological studies, epidemiological investigations, and environmental exposure data. This information is presented to provide public health officials, physicians, toxicologists, and other interested individuals and groups with (1) an overall perspective of the toxicology of silver and (2) a depiction of significant exposure levels associated with various adverse health effects.

Silver occurs naturally in several oxidation states. The most common are elemental silver (0 oxidation state) and the monovalent silver ion (+l oxidation state). Most of the toxicological studies of silver have investigated these chemical forms of the element. Other possible oxidation states of silver are +2 and +3, however, no toxicological studies were located that researched the health effects of silver compounds with these oxidation states. Most occupational exposures to silver occur through inhalation of silver-containing dusts or dermal exposure to photographic compounds. Published studies on human inhalation of silver are based predominantly on exposure to elemental silver, silver nitrate, and silver oxide. Human oral data come from information on medicines containing silver, such as silver acetate-containing antismoking lozenges, breath mints coated with silver, and silver nitrate solutions for treating gum disease. Animal studies usually are based on exposure to silver nitrate and silver chloride in drinking water. Humans may be dermally exposed to silver through the use of silver-containing processing solutions for radiographic and photographic materials, dental amalgams, and medicines (e.g., silver sulphadiazine cream and solutions for treating burns).

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the data in this section are organized first by route of exposure -- inhalation, oral, and dermal -- and then by health effect -- death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods -- acute, intermediate, and chronic. Levels of significant exposure for each exposure route and duration (for which data exist) are presented in tables and illustrated in figures. The

points in the figures showing no-observed-adverse-effect levels (NOAELS) or lowest-observed-adverse-effect levels (LOAELS) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear, determine whether or not the intensity of the effects varies with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown on the tables and graphs may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons or with the identification of persons with the potential to develop such disease may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with response actions at Superfund sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) are of interest to health professionals and citizens alike.

Estimates of exposure posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer end point for each exposure duration. MRLs include adjustments to reflect human variability and, where appropriate, the uncertainty of extrapolating from laboratory animal data to humans. Although methods have been established to derive these levels (Barnes et al. 1987; EPA 1989a), uncertainties are associated with the techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of these procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular or musculoskeletal effects in humans or animals after inhalation exposure to silver or silver compounds.

2. HEALTH EFFECTS

Respiratory Effects. Respiratory effects have been observed infrequently in humans following inhalation of silver compounds. In one case report of a worker who had become ill 14 hours after he had been working with molten silver ingots, symptoms were limited primarily to the respiratory system (Forycki et al. 1983). Unfortunately, the concentration and chemical composition of the silver in the work room air were not known, and the history of exposure to silver prior to this incident was not reported. The initial symptoms seen in this patient included audible crackles during breathing, rapid pulse, low oxygen content of capillary blood, and scattered thickening of the lungs observed in chest radiograms. The patient's symptoms progressed to acute respiratory failure, from which the patient eventually recovered fully.

Occupational exposure to silver dusts can also lead to respiratory irritation (Rosenman et al. 1979, 1987). One occupational study describes a group of 30 employees of a manufacturing facility involved in the production of silver nitrate and silver oxide (Rosenman et al. 1979). The average air level of these silver compounds over the duration of the workers' exposure was not estimated. However, personal air monitoring conducted 4 months previous to the study determined an 8 hour time-weighted average (TWA) concentration range of 0.039 to 0.378 mg silver/m^3. Duration of employment ranged from less than one, to greater than ten years. Twenty-five of the 30 workers complained of upper respiratory irritation (sneezing, stuffiness, and running nose or sore throat) at some time during their employment, with 20 out of 30 complaining of cough, wheezing, or chest tightness. Chest radiograms and results of clinical examination of respiratory function were predominantly normal, with no demonstrated relationships between abnormalities and duration of employment. Similar complaints were recorded for workers involved in the manufacture of silver metal powders, although the workers were concurrently exposed to acids, hydroquinone, formaldehyde, caustics, solvents, and cadmium (Rosenman et al. 1987).

Acute (2-8 hours) inhalation of an aerosol containing colloidal silver by rabbits (whole body exposure, concentrations not given) has been reported to lead to ultrastructural damage and disruption of cells of the tracheal epithelium (Konradova 1968).

Gastrointestinal Effects. Abdominal pain has also been reported by workers exposed to silver nitrate and oxide in the workplace (Rosenman et al. 1979). The pain was described as "burning in quality and relieved by antacids" and was reported in 10 out of 30 workers examined. Exposure levels were estimated to be between 0.039 and 0.378 mg silver/m^3. No information on chemical form or particle size was provided. Duration of employment ranged from less than one, to greater than ten years. This symptom correlated significantly with blood silver levels, indicating that those workers exposed to higher levels of airborne silver nitrate and/or oxide are more likely to suffer gastrointestinal pain.

No studies were located regarding gastrointestinal effects in animals following inhalation exposure to silver or silver compounds.

Hematological Effects. Blood counts were reported to be normal in all individuals observed in the occupational study of silver-exposed workers conducted by Rosenman et al (1979) with the exception of one individual with an elevated hemoglobin level. In a study by Pifer et al. (1989), silver reclamation workers chronically exposed to insoluble silver compounds (e.g., the silver halides) exhibited a marginal decrease in red blood cell count, as well as an increase in mean corpuscular volume. However, the toxicological significance of these findings is unclear.

No studies were located regarding hematological effects in animals following inhalation exposure to silver or silver compounds. Despite the lack of supportive animal data, occupational exposure findings suggest that hematological effects are not a sensitive indicator of silver toxicity.

Hepatic Effects. A study that measured levels of several liver enzymes (alanine amino transferase, aspartate amino transferase, gamma glutamyl transferase, and alkaline phosphatase) found no significant differences between workers exposed to silver and insoluble silver compounds and those with no history of silver exposure (Pifer et al. 1989).

No studies were located regarding hepatic effects in animals following inhalation exposure to silver or silver compounds.

Renal Effects. Occupational exposure to silver metal dust has been associated with increased excretion of a particular renal enzyme (N-acetyl-β-D glucosaminidasej, and with decreased creatinine clearance (Rosenman et al. 1987). Both of these effects are diagnostic of marginally impaired renal function. However, the workers in this study were also exposed to cadmium, which was detected in the urine of 5 of the 27 workers studied. Cadmium is known to be nephrotoxic; differentiation of the effects of the two metals in the kidney is not possible with the data presented. Therefore, no conclusion can be drawn regarding renal effects of silver based on this study.

No studies in animals were located which support the observation of renal effects in the Rosenman et al (1987) study. Studies in animals have focused only on the deposition of silver in the kidney following oral exposure (Olcott 1947; 1948) and renal function tests were not conducted.

Dermal/Ocular Effects. Skin and ocular burns, caused by contact with silver nitrate, have been reported in workers (Moss et al. 1979; Rosenman et al 1979).

Granular deposits were observed in the conjunctiva and cornea of the eyes of 20 out of the 30 workers in the occupational study of Rosenman et al.

(1979), and subjective determination of the degree of silver deposition in the conjunctiva correlated with the duration of employment (see also Moss et al. 1979). Furthermore, the amount of deposition in the eyes was found to correlate significantly with reports of changes in skin color and decreased night vision. The complaint of decreased night vision was also recorded in a study of workers involved in the manufacture of metal silver powders (Rosenman et al. 1987).

An investigation of silver reclamation workers found that 21% and 25% exhibited conjunctival and cornea1 argyrosis (silver staining or deposition), respectively (Pifer et al. 1989). Moreover, 74% of the subjects exhibited some degree of internal nasal-septal pigmentation. However, no association was observed between silver deposition and ocular impairment.

In another report describing the same cohort of workers as studied by Rosenman et al. (1979), Moss et al. (1979) conducted electrophysiological and psychophysiological studies of the eyes of 7 of the 10 workers who had complained of decreased night vision. No functional deficits were found in the vision of these workers.

The relative contributions of dermal/ocular absorption, ingestion, and inhalation of silver compounds to the development of these ocular deposits and skin color changes are not known. However, granular deposits containing silver have been observed to-develop in various ocular tissues of animals following ingestion of silver compounds, and it is likely that systemic absorption following inhalation exposure also results in silver deposition (Matuk et al 1981; Olcott 1947; Rungby 1986). The possibility remains that the deposits were in some proportion caused by direct exposure of the eyes to airborne silver compounds.

No studies were located regarding dermal or ocular effects in animals following inhalation exposure to silver or silver compounds.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to silver or silver compounds.

2.2.1.3 Immunological Effects

2.2.1.4 Neurological Effects

2.2.1.5 Developmental Effects

2.2.1.6 Reproductive Effects

2.2.1.7 Genotoxic Effects

2.2.1.8 Cancer

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans following oral exposure to silver or silver compounds.

Death has been observed in rats following ingestion of colloidal silver and inorganic silver compounds. In each case the level of silver was very high. For example, death was reported in rats (number not specified) following acute oral ingestion of silver colloid (Dequidt et al. 1974). In another study, Walker (1971) reported deaths in 3 of 12 rats during a 2-week exposure to silver nitrate in drinking water. Cause of death was not reported in either of these studies. However, the rats in the Walker (1971) study were observed to decrease their water intake "precipitously" beginning on the 1st day of exposure, and survivors were generally described as "poorly groomed and listless" at the end of the exposure. No lethality occurred in a lower dose group.

Death was also reported in an unspecified number of rats receiving 222.2mg silver/kg/day as silver nitrate in drinking water over a longer duration (Matuk et al. 1981). The deaths began occurring approximately 23 weeks into 37-week experiment during which the exposed animals also showed a decreased weight gain compared to animals receiving only water. The highest NOAEL values and all reliable LOAEL values for death in each species and duration are recorded in Table 2-l and plotted in Figure 2-l.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after oral exposure to silver or silver compounds.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to silver or silver compounds.

One study reported enlargement of the left ventricle in rats following 9-29 months of oral exposure to silver nitrate or silver chloride in drinking water (Olcott 1950). Left ventricle size (expressed as a ratio of ventricle weight to body weight) increased with exposure,duration, and showed a tendency to increase with dose of silver. The authors suggest that the increase in ventricle size could be caused by hypertension, but no blood pressure measurements were performed. Gross and histopathological examination of the tissues revealed only a few scattered granular deposits in the heart. The effect on left ventricle size was seen at a dose of 88.9 mg silver/kg/day;

TABLE 2-1. Levels of Significant Exposure to Silver* - Oral

Figure Key	Species	Route	Exposure Frequency/ Duration	Effect	NOAEL (mg Ag/kg/day)	LOAEL (Effect) Less Serious (mg Ag/kg/day)	LOAEL (Effect) Serious (mg Ag/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	NS	4 d 1x/d				1680	Dequidt et al. 1974
2	Rat	(W)	2 wk 7d/wk		181.2		362.4[a] (3/12)	Walker 1971
INTERMEDIATE EXPOSURE								
Systemic								
3	Rat	(W)	37 wk 7d/wk	Other		222.2[b] (< weight gain)		Matuk et al. 1981
Neurological								
4	Mouse	(W)	125 d 7d/wk			18.1[c] (hypoactivity)		Rungby and Danscher 1984

*Presented as elemental silver.

[a]Converted to an equivalent concentration of 2,589 ppm in water for presentation in Table 1-4.
[b]Converted to an equivalent concentration of 1,587 ppm in water for presentation in Table 1-4.
[c]Converted to an equivalent concentration of 95 ppm in water for presentation in Table 1-4.

mg/kg/day = milligrams per kilogram per day; NS = not specified; d = day; (W) = drinking water; wk = week; x = time(s); < = decreased.

FIGURE 2-1. Levels of Significant Exposure to Silver - Oral

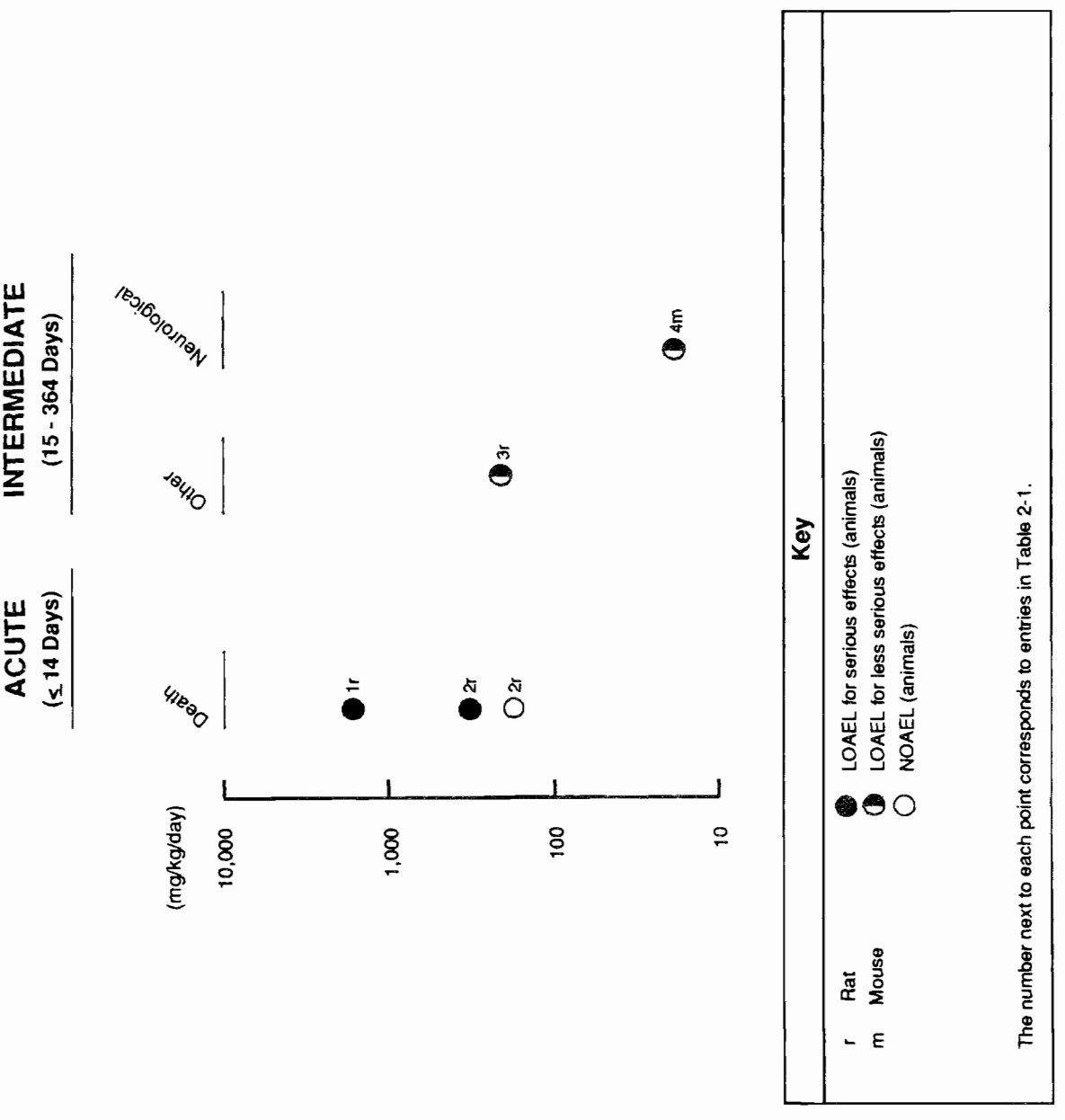

FIGURE 2-1. Levels of Significant Exposure to Silver - Oral

however, limitations of the study such as poor experimental design and inadequate reporting of methods preclude use of these data to predict equivalent levels of exposure in humans.

Dermal/Ocular Effects. Gray or blue-gray discoloration of the skin has been observed in individuals that have ingested both metallic silver and silver compounds in small doses over periods of months to years. Silver containing granules have been observed during histopathologic examination of the skin of these individuals. The condition is termed "argyria." Unfortunately, only rough estimates of the amount of silver ingested were located, and therefore precise levels of exposure resulting in discoloration cannot be established.

Case histories of argyria have been published concerning individuals who had ingested silver through excessive use of antismoking lozenges containing silver acetate, silver nitrate solutions for the treatment of gum disease, breath mints coated with metallic silver, and capsules containing silver nitrate for the relief of gastrointestinal "discomfort" (Aaseth et al. 1981; Blumberg and Carey 1934; East et al. 1980; MacIntyre et al 1978; Marshall and Schneider 1977; Shelton and Goulding 1979; Shimamoto and Shimamoto 1987). In general, quantitative data were nonexistent or unreliable and could not be used to establish LOAELs. The only common symptom among these cases was the resulting gray pigmentation of the skin of primarily sun-exposed regions. Examination of skin biopsies. from these individuals at the light microscopic level revealed granular deposits in the dermis. The granules were distributed throughout the dermis, but were particularly concentrated in basement membrane and elastic fibers surrounding sweat glands. The granules have been observed to contain silver (Bleehen et al. 1981; MacIntyre et al. 1978).

Ingestion of silver nitrate and silver chloride will also cause deposition of silver granules in the skin of animals (Olcott 1948; Walker 1971). However, skin discoloration in animals following exposure to these silver compounds has not been studied specifically, and the level of deposition that leads to skin discoloration in humans cannot be established based on existing animal data. Granules are also observed in the eyes of rats exposed to silver nitrate in drinking water at doses that cause general deposition in other tissues (Matuk et al. 1981; Olcott 1947; Rungby 1986). The number of deposits in the eyes is related to the degree of yellow-to-darkgray pigmentation observed at gross examination, which in turn is related to the duration of exposure.

Other Systemic Effects. Rats receiving 222.2 mg silver/kg/day in their drinking water lost weight over a 37 week exposure period. Weight loss first appeared about 23 weeks into the experiment, and the authors observed that several animals that lost weight rapidly died. Body weight in the surviving experimental animals was an average of 50% less than that of control rats

drinking only distilled water over the same exposure period (Matuk et al. 1981).

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals following oral exposure to silver or silver compounds.

2.2.2.4 Neurological Effects

Several reports describe the deposition of what are assumed to be silvercontaining granules in tissues of the central nervous system. One report describes such granules in certain areas of the brain of an argyric woman at autopsy (Landas et al. 1985) who had used nose drops containing silver nitrate (concentration not specified) for an unspecified duration. The areas of the brain described as containing silver in the Landas et al (1985) study are known to have more direct exposure to blood-borne agents than other areas (e.g., the "circumventricular organslt, and the paraventricular and supraoptic nuclei of the hypothalamus). Unfortunately, the study examines only these specialized areas, and so does not provide complete information on the distribution of silver throughout the brain. There is no evidence that clearly relates the existence or deposition of these granules to a neurotoxic effect of silver exposure.

However, one study has found that 20 female mice exposed to silver nitrate in drinking water for 4 months, and observed to have such deposits in the central nervous system, were less active (hypoactive) than unexposed controls (Rungby and Danscher 1984). Activity was easured using a blind assay. The highest concentration of granular deposits occurred in certain areas involved in motor control (i.e., red nucleus, deep cerebellar nuclei, and motor nuclei of the brainstem), with lesser amounts observed in the basal ganglia, the anterior olfactory nucleus, and in the cortex in general. A specific relationship between the deposition of granules in these brain areas following silver ingestion and the decrease in gross activity has not been established. The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration are recorded in Table 2-l and plotted in Figure 2-1.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans or animals after oral exposure to silver or silver compounds.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to silver or silver compounds.

No diminution of fertility was observed in male rats exposed,. for up to 2 years, to 88.9 mg silver/kg/day as silver nitrate or silver chloride in drinking water (Olcott 1948). Appearance of spermatozoa was normal, and no silver deposits were observed in the testes. Unfortunately, poor experimental design and reporting of methods preclude use of these data in determining a no effect level for male reproductive effects.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to silver or silver compounds.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to silver or silver compounds.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding death in humans following dermal exposure to silver or silver compounds.

Mortality following dermal application of silver nitrate has been investigated in guinea pigs (Wahlberg 1965). The investigators applied 2.0 mL of a 0.239 molar solution of silver nitrate, in water by skin depot to 3.1 cm^2 of skin for 8 weeks. No deaths were recorded; however, during the exposure period the guinea pigs ceased to gain weight. In concurrent investigations of equimolar amounts of other metal salts using the same methods, mercuric chloride and cobalt chloride caused the death of more than half of the test animals.

The NOAEL value for death is recorded in Table 2-2.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or ocular effects in humans or animals after dermal exposure to silver or silver compounds.

Dermal. Medical case histories indicate that dermal exposure to silver or silver compounds for extended periods of time can lead to local skin discoloration similar in nature to the generalized pigmentation seen after repeated oral exposure. However, the amount of silver and the duration of time required to produce this effect cannot be established with the existing

TABLE 2-2. Levels of Significant Exposure to Silver* - Dermal

Figure Key	Species	Exposure Frequency/ Duration	Effect	NOAEL (mg Ag/kg/day)	LOAEL (Effect) Less Serious (mg Ag/kg/day)	LOAEL (Effect) Serious (mg Ag/kg/day)	Reference
INTERMEDIATE EXPOSURE							
Death							
1	Gn pig	8 wk 7d/wk (skin depot)		137.13			Wahlberg 1965
Systemic							
2	Gn pig	8 wk 7d/wk (skin depot)	Other		137.13 (< weight gain)		Wahlberg 1965

*Presented as elemental silver.

mg/kg/day = milligrams per kilogram per day; Gn pig = guinea pig; wk = week; d = day; < = decreased.

information (Buckley 1963; McMahon and Bergfeld 1983). Moreover, adverse effects such as argyria have not been associated with the use of silver sulphadiazine as a bactericidal agent (Fox et al. 1969). No studies were located regarding dermal effects in animals after dermal exposure to silver or silver compounds.

Other Systemic Effects. Decreased body weight gain was observed in guinea pigs following application of 81 mg silver nitrate (2 mL of a 0.239 M solution) to 3.1 cm^2 of skin. At the end of 8 weeks, the silver nitrate-exposed guinea pigs weighed approximately 10-20% less than unexposed controls and controls exposed to distilled water (Wahlberg 1965).

2.2.3.3 Immunological Effects

Medical case histories describe mild allergic responses attributed to repeated dermal contact with silver and silver compounds (Catsakis and Sulica 1978; Hey1 1979; Marks 1966). Sensitization occurred in response to contact with powdered silver cyanide, radiographic processing solutions, and apparently to silver in dental amalgam. The duration of exposure ranged from 6 months in a worker exposed to silver cyanide, 10 years for a woman employed as a radiograph processor, to 20 years for a woman whose allergy had apparently been caused by dental fillings. The concentration of silver that caused these allergic responses is not known. No studies were located' regarding immunological effects in animals after dermal exposure to silver or silver compounds.

No studies were located regarding the following health effects in humans and animals after dermal exposure to silver or silver compounds.

2.2.3.4 Neurological Effects

2.2.3.5 Developmental Effects

2.2.3.6 Reproductive Effects

2.2.3.7 Genotoxic Effects

2.2.3.8 Cancer

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Studies in humans regarding the absorption of silver following inhalation exposure are limited to occupational studies and a case study. It is assumed

that the predominant routes of exposure to silver in the workplace are inhalation and dermal, with the dermal route being more important when prolonged contact with silver in solution occurs (as in photographic processing). Given this assumption, existing studies suggest that silver and silver compounds can be absorbed when inhaled, although the degree of absorption, both absolute and relative to the degree of dermal absorption, is not known.

A case study involving an accidental exposure of one worker to radiolabeled silver metal during a nuclear reactor mishap supports the assumption that absorption of silver metal dust can occur following inhalation exposure (Newton and Holmes 1966). Radioactive silver was measured using whole-body gamma-ray spectrometry beginning two days after a one-time inhalation exposure and continued for up to 200 days. Localization of silver in the liver, and detection in feces indicated that passage through the lungs had occurred. Unfortunately this study did not measure exposure, and therefore absorption could not be quantitated.

Twelve out of 30 workers in a chemical manufacturing facility which produced silver nitrate and silver oxide were found to have blood silver levels greater than the detection limit of 0.6 μg silver/100 mL blood (Rosenman et al. 1979). Exposure levels were estimated to range from 0.039 to 0.378 mg silver/m^3. DiVincenzo et al. (1985) examined the silver content of blood, urine, and feces of workers exposed to TWA levels of 0.001 to 0.1 mg/m^3 insoluble silver in a photographic materials manufacturing facility. The identity of the specific silver compounds to which the workers were exposed was not reported. In exposed workers, silver was detected in 80% of the blood samples and in 100% of the fecal samples (mean concentrations of 0.011 μg/ml and 15 μg/g, respectively). Silver was detected in 2 of 35 (6%) urine samples from exposed workers with a mean concentration of 0.009 μg/g. Silver was also detected in the feces of controls (not exposed occupationally) at a mean concentration of 1.5 μg/g. Although these studies suggests that silver compounds are absorbed from the lungs, unknown exposure levels and lack of compound identification prevent estimation of extent or rate.

A study in dogs indicates that absorption of inhaled metallic silver particles with a median aerodynamic diameter of approximately 0.5 μm is extensive, and is not dependent upon particle size (Phalen and Morrow 1973). Absorption was measured in one dog that remained anesthetized during the entire period between exposure and sacrifice. In this dog, 3.1% (0.8 μg) of the deposited material was dissolved, transported out of the lungs, and was found mostly in liver and blood 6 hours after exposure; a 1 μg/cm^2/day absorption rate for metallic silver was estimated by the authors. up to 90% of the deposited silver was estimated to be absorbed into the systemic circulation based on all experimental data. Clearance from the lung to the blood was triphasic, with half-lives of 1.7, 8.4, and 40 days.

2.3.1.2 Oral Exposure

Based on medical case studies and experimental evidence in humans, many silver compounds, including silver salts and silver-protein colloids, are known to be absorbed by humans across mucous membranes in the mouth and nasal passages, and following ingestion. Absorption of silver acetate occurred following ingestion of a 0.08 mg/kg/day dose of silver acetate containing radiolabeled silver (^{110m}Ag). Approximately 21% of the dose was retained in the body at 1 week (East et al. 1980; MacIntyre et al. 1978). Furthermore, the occurrence of generalized argyria in a woman who repeatedly applied silver nitrate solution to her gums (Marshall and Schneider 1977) suggests that absorption across the oral mucosa can occur. Information concerning the rate of oral absorption in humans was not located.

The extent of absorption of an administered dose has been found to be associated with transit time through the gastrointestinal tract; the authors report that this may explain some of the interspecies differences in silver retention observed 1 week after exposure (see Table 2-3). The faster the transit time, the less silver is absorbed (Furchner et al. 1968). Transit times vary from about 8 hours in the mouse and rat to approximately 24 hours in the monkey, dog, and human (Furchner et al. 1968).

2.3.1.3 Dermal Exposure

Several silver compounds appear to be absorbed through the intact skin of humans, although the degree of absorption is thought to be low. For example, silver thiosulfate penetrated the intact skin of a photochemical worker via the eccrine sweat glands and deposited in the dermis, leading to the development of localized argyria within 6 months of exposure (Buckley 1963). Silver compounds also are absorbed through the damaged skin of humans. Silver was detected in the urine, blood, and body tissues of humans with seriously burned skin following treatment with topical preparations containing 0.5% silver nitrate to prevent bacterial infection (Bader 1966). The levels of silver found in one of the individuals studied by Bader (1966) were 0.038 and 0.12 ppm for urine and blood, respectively, and ranged from below detection in lung and brain to 1,250 ppm in skin. Snyder et al. (1975) estimated that less than 1% of dermally-applied silver compounds are absorbed through the intact skin of humans.

Absorption of silver nitrate across intact skin has been demonstrated in guinea pigs and is similar to that of intact human skin (Wahlberg 1965). The amount absorbed was estimated to be approximately 1% of the applied dose within 5 hours of exposure. Silver administered in the form of silver sulphadiazine cream was minimally absorbed through both the intact and burned skin of rats and distributed throughout the body (Sano et al. 1982). The absorption of silver increased through burned skin after blister removal. The authors did not determine the percentage of the applied dose that was absorbed (Sano et al. 1982).

TABLE 2-3. Interspecies Differences in the Oral Absorption of Silver

Species	Silver Compound	Body Weight (g)	Administered Dose (mg/kg)	Dose Retention at 1 Week (%)
Mouse[a]	$^{110m}AgNO_3$	26.6	0.0011[c]	<1
Rat[a]	$^{110m}AgNO_3$	355.0	0.0002[c]	≤1
Monkey[a]	$^{110m}AgNO_3$	6,730.0	0.00001[c]	<1
Dog[a]	$^{110m}AgNO_3$	13,330.0	0.000005[c]	≈10
Human[b]	$AgCH_3CO_2$	58,600.0	0.08	21

[a]Furchner et al. 1968.
[b]MacIntyre et al. 1978.
[c]Dose conversion: Specific activity was 8.7 Ci/g silver nitrate
8.7 Ci/g = 8.7 x 10^6 μCi/1 x 10^3 mg = 8,700 μCi/mg.

Administered dose (μCi)/8,700 μCi/mg = mg silver nitrate
mg silver nitrate/kg body weight/day = mg/kg/day.

Mouse: 0.25/8,700 = 2.87 x 10^{-5} mg silver nitrate
2.87 x 10^{-5} mg/0.0266 kg/day = 0.001 mg/kg/day.

Rat: 0.5/8,700 = 0.0001 mg silver nitrate
0.0001mg/0.355 kg/day = 0.0002 mg/kg/day.

Monkey: 0.6/8,700 = 0.0001 mg silver nitrate
0.0001 mg/6.73 kg/day = 0.00001 mg/kg/day.

Dog: 0.6/8,700 = 0.0001 mg silver nitrate
0.0001 mg/13.33 kg/day = 0.000005 mg/kg/day.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Limited information was located concerning the distribution of silver in humans following inhalation of elemental silver or silver compounds. Using whole-body spectrometer measurements obtained from a person accidently exposed to radiolabeled silver, Newton and Holmes (1966) estimated that 25% of the detectable ^{110m}Ag was distributed to the liver between 2 and 6 days after exposure.

Phalen and Morrow (1973) reported that 96.9%, 2.4%, and 0.35% of the dose initially deposited in the lungs of a dog following intratracheal administration was detected in the lungs, liver, and blood, respectively, 6 hours after exposure. The remaining silver was detected in the gall bladder and bile (0.14%), intestines (0.10%), kidneys (0.06%), and stomach (0.02%). The distribution of metallic silver (expressed as a percentage of the initial amount deposited) 225 days after exposure differed from that at 6 hours, with the majority of the metal detected in the liver (0.49%), brain (0.035%), gall bladder and bile (0.034%), intestines (0.028%), lungs and trachea (0.019%), bone (0.014%), stomach and contents (0.012%), heart (0.009%), and muscle (0.007%). The distribution to tissues other than the lungs is similar at 6 hours and 225 days if silver in the lungs is not considered. At both time points the majority of the silver is found in the liver (approximately 77% of the total body silver excluding lung content).

2.3.2.2 Oral Exposure

The distribution of silver to various body tissues depends upon the route and quantity of silver administered and its chemical form. An oral dose of silver, following absorption, undergoes a first pass effect through the liver resulting in excretion into the bile, thereby reducing systemic distribution to body tissues (Furchner et al. 1968). The subsequent distribution of the remaining silver is similar to the distribution of silver absorbed following exposure by the inhalation and dermal routes and following intramuscular or intravenous injection.

Silver distributes widely in the rat following ingestion of silver chloride (in the presence of sodium thiosulfate) and silver nitrate in drinking water (at 88.9 mg silver/kg/day for silver nitrate) (Olcott 1948); The amount of silver in the various tissues was not measured, although qualitative descriptions of the degree of pigmentation were made. High concentrations were observed in the tissues of the reticuloendothelial system in the liver, spleen, bone marrow, lymph nodes, skin, and kidney. Silver was also distributed to other tissues including the tongue, teeth, salivary glands, thyroid, parathyroid, heart, pancreas, gastrointestinal tract, adrenal glands, and brain. Within these tissues advanced accumulation of silver

particles was found in the basement membrane of the glomeruli, the walls of blood vessels between the kidney tubules, the portal vein and other parts of the liver, the choroid plexus of the brain, the choroid layer of the eye, and in the thyroid gland (Olcott 1948; Moffat and Creasey 1972; Walker 1971).

Approximately 18-19% of a single oral dose of silver acetate was retained in the body of a human 8-30 weeks after exposure (East et al. 1980; Macintyre et al. 1978). This amount is 10% greater than that retained in dog tissues 20 weeks after a single oral dose (Furchner et al. 1968).

2.3.2.3 Dermal Exposure

Following the topical application of silver nitrate for the treatment of burns in two humans, silver was distributed to the muscles (0.03-2.3 ppm), liver (0.44 ppm), spleen (0.23 ppm), kidney (0.14 ppm), heart (0.032-0.04 ppm), and bones (0.025 ppm) (Bader 1966). No studies were located that quantitated the distribution of silver in animals following dermal exposure to silver or its compounds. However, Sano et al. (1982) detected silver in the same tissues of rats following topical application of silver sulphadiazine cream.

2.3.2.4 Other Routes of Exposure

In rats, silver was unevenly distributed in organs and tissues following intravenous or intramuscular injection of radiolabeled metallic silver and/or silver nitrate, respectively. The highest concentrations were found, in decreasing order, in the gastrointestinal tract, liver, blood, kidney, muscle, bone, and skin following intramuscular injection (Scott and Hamilton 1950). Following intravenous injection the highest concentrations were found, in decreasing order, in the liver, pancreas, spleen, and plasma (Klaassen 1979a). As is shown in Table 2-4, the proportion of the dose distributed to the tissues is positively correlated with the dose administered (Scott and Hamilton 1950).

Silver is cleared from the system via the liver (Furchner et al. 1968; Scott and Hamilton 1950). Deposition of uncleared silver can occur along the renal glomerular basement membrane (Creasey and Moffat 1973; Danscher 1981; Ham and Tange 1972; Moffat and Creasey 1972) and mesangium (Day et al. 1976), and in the Kupffer cells and the sinusoid endothelium cells of the liver (Danscher 1981). Silver has also been detected intra- and extracellularly in the skin and mucosa of the tongue, in the chromaffin cells, cells of the zona glomerulosa, and zona fasciculata of the adrenal glands, and in the exocrine and endocrine sections of the pancreas (Danscher 1981).

In rodents, silver has been shown to cross the placenta and to enter the fetuses following an intraperitoneal injection of silver lactate to the mothers (Rungby and Danscher 1983a). Silver was detected in the liver and brain tissues of rat fetuses (Danscher 1981; Rungby and Danscher 1983a).

TABLE 2-4. Distribution in Rats at Six Days of Intramuscularly Administered Radioactive Silver Tracer Dose when Administered Alone and when Coadministered with Additional Silver as Silver Nitrate

	Percent of Tracer Dose Recovered		
Tissue	Tracer Dose Alone	Silver Nitrate 0.4 mg/kg/day	Silver Nitrate 4.0 mg/kg/day
Heart and lungs	0.06	0.13	0.59
Spleen	0.01	0.13	2.69
Blood	0.5	0.95	3.03
Liver	0.36	2.24	33.73
Kidney	0.07	0.92	0.63
Gastrointestinal tract	1.12	4.22	8.21
Muscle	0.27	0.56	2.39
Bone	0.18	0.35	2.20
Skin	0.24	0.67	7.39
Urine	0.64	0.88	1.82
Feces	96.56	88.95	37.33

note: A small (unspecified) dose of radioactively labeled silver was used as a tracer. The distribution of silver is reported as percentage of tracer dose radioactivity recovered per organ.

Source: Scott and Hamilton 1950

2.3.3 Metabolism

The deposition of silver in tissues is the result of the precipitation of insoluble silver salts, such as silver chloride and silver phosphate. These insoluble silver salts appear to be transformed into soluble silver sulfide albuminates, to bind to or form complexes with amino or carboxyl groups in RNA, DNA, and proteins, or to be reduced to metallic silver by ascorbic acid or catecholamines (Danscher 1981). The blue or gray discoloration of skin exposed to ultraviolet light in humans with argyria may be caused by the photoreduction of silver chloride to metallic silver. The metallic silver is then oxidized by tissue and bound as black silver sulfide (Danscher 1981). Buckley et al. (1965) identified silver particles deposited in the dermis of a woman with localized argyria as being composed of silver sulfide.

In rats, silver deposits in internal organs such as the kidney, have also been identified as the sulfide (Berry and Galle 1982). Under conditions of exposure to high doses of selenium, the sulfur can be replaced by selenium (Berry and Galle 1982). The deposition of silver in the kidney was increased under conditions of high selenium exposure. This may be important in the development of argyria in people exposed to silver who ingest foods that contain large amounts of selenium (See Section 2.7).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

The clearance of radioactive silver metal dust in a man who was accidentally exposed illustrated the rapid removal of silver from the lungs primarily by ciliary action, with subsequent ingestion and ultimate elimination in the feces (Newton and Holmes 1966). Lung clearance fit a biexponential profile, with biological half-lives of 1 and 52 days. Radioactive silver was detected in the feces up to 300 days after exposure, but was not detected in urine samples (collected up to 54 days after exposure).

Chronic exposure of workers to unidentified silver compounds resulted in the detection of silver in 100% of the fecal samples and 6% of the urine samples (DiVincenzo et al. 1985). This occupational exposure is assumed to have occurred primarily by the inhalation route.

In dogs, lung clearance of metallic silver particles (average aerodynamic diameter of 0.5μ) following intra-tracheal intubation was accompanied by an increase in silver concentration in the area of the stomach and liver. The increase in silver concentration in the stomach suggests that some proportion of the silver particles are cleared by the mucociliary escalator and swallowed. However, the predominant route of clearance from the lung appeared to be through dissolution of the silver and transport through the blood. The

silver was apparently carried by the blood to the liver, with little cleared via the mucociliary passages (Phalen and Morrow 1973). Approximately 90% of the inhaled dose was excreted in the feces within 30 days of exposure. Clearance of deposited silver particles from the lung fit a triexponential profile, with biological half-lives of 1.7, 8.4, and 40 days, accounting for 59, 39, and 2% of the radioactivity excreted, respectively. Clearance of absorbed silver from the liver fit a biexponential profile with biological half-lives of 9.0 and 40 days accounting for 97% and 3% of the radioactivity excreted, respectively (Phalen and Morrow 1973).

2.3.4.2 Oral Exposure

Following oral exposure to silver acetate in humans, silver is eliminated primarily in the feces, with only minor amounts eliminated in the urine (East et al. 1980). The rate of excretion is most rapid within the first week after a single oral exposure (East et al. 1980). Whole-body retention studies in mice and monkeys following oral dosing with radiolabeled silver nitrate indicate that silver excretion in these species follows a biexponential profile with biological half-lives of 0.1 and 1.6 days in mice and 0.3 and 3 days in monkeys. In similarly exposed rats and dogs, silver excretion followed a triexponential profile with biological half-lives of 0.1, 0.7, and 5.9 days in rats and 0.1, 7.6, and 33.8 days in dogs (Furchner et al. 1968). Data for whole body clearance of silver at two days after exposure for these four species are presented in Table 2-5 (Furchner et al. 1968). Transit time through the gut may explain some of these interspecies differences in silver excretion. Transit time is approximately 8 hours in mice and rats, and approximately 24 hours in dogs and monkeys (Furchner et al. 1968). Animals excrete from 90% to 99% of an administered oral dose of silver in the feces within 2 to 4 days of dosing (Furchner et al. 1968; Jones and Bailey 1974; Scott and Hamilton 1950). Excretion in the feces is decreased and deposition in tissues, such as the pancreas, gastrointestinal tract, and thyroid, is increased when saturation of the elimination pathway in the liver occurs as a result of chronic or high level acute exposure to silver (see Table 2-4) (Constable et al. 1967; Olcott 1948; Scott and Hamilton 1950).

2.3.4.3 Dermal Exposure

No studies were located concerning the excretion of silver by humans or animals following dermal exposure to elemental silver or silver compounds. Once absorption through the skin and distribution to bodily tissues occurs, it can be expected that elimination would be similar to that of silver absorbed via oral or inhalation exposure, that is, primarily via the feces, with minimal amounts excreted in the urine.

2.3.4.4 Other Routes of Exposure

Whole body retention studies in mice, rats, monkeys, and dogs following intravenous injection of radiolabeled silver nitrate indicate that silver

excretion in these species follows a triexponential profile. (Furchner et al. 1968). For mice and monkeys, this differs from the biexponential profile seen following oral exposure. Whole body clearance following intravenous exposure was slower than clearance following oral exposure in each of the four species observed. In addition, the difference in clearance rate between species was more dramatic. Clearance at 2 days post-exposure ranged from 15% in the dog to 82% in the mouse (see Table 2-5) (Furchner et al. 1968).

Silver removal from the liver by biliary excretion was demonstrated by Scott and Hamilton (1950). Control rats and rats with ligated bile ducts were administered radioactive metallic silver by intramuscular injection. In rats with ligated bile ducts, excretion of silver in the feces was 19%, compared to 97% in controls. Deposition in the liver of rats with ligated bile ducts was 48% and 2.5% in the gastrointestinal tract compared to 0.36% and 1.12%, respectively in the controls (Scott and Hamilton 1950). Klaassen (1979b) determined that biliary excretion accounted for between 24% and 45% of the silver administered to rats. The concentration of silver in the bile was estimated to be between 16 and 20 times greater than that in plasma. An increase in the bile/liver tissue ratio (μg/ml per μg/g) from 4.2 to 6.4 indicates that more silver is concentrated in the bile as the dose of silver increases. It is believed that active transport is involved in the transfer of silver from the plasma to the bile (Klaassen 1979b). There are apparently interspecies differences in this transport process. The variability in the extent of biliary silver excretion appears to be related to the ability of the liver to excrete silver into the bile, not to the ability of the silver to pass between the plasma and the liver. Rats excreted silver in the bile at 10 times the rate of rabbits. Dogs excreted silver in the bile at a rate lower than that of rabbits (Klaassen 1979b). Dogs had the highest amount of silver retained in the liver (2.9 μg silver/g), as compared to the rabbit (2.13 ,μg silver/g) and rat (1.24 μg silver/g).

2.4 RELEVANCE TO PUBLIC HEALTH

The one clinical condition that is known in humans to be attributable to long-term exposure to silver and silver compounds is a gray or blue-gray discoloring of the skin (argyria). Argyria may occur in an area of repeated or abrasive dermal contact with silver or silver compounds, or more extensively over widespread areas of skin and the conjunctiva of the eyes following long-term oral or inhalation exposure. Argyria was common around the turn of the century when many pharmaceutical preparations contained silver (Hill et al. 1939). It is much less common today, probably because most current medications containing silver are for dermal application only. Case reports in humans have reported that repeated dermal contact with silver compounds may in some cases lead to contact dermatitis, and a generalized allergic reaction to silver.

Evidence from both human and animal studies indicates that inhalation of silver compounds can irritate the respiratory pathway. Occupational studies

TABLE 2-5. **Interspecies Differences in the Clearance of Silver Compounds**[a]

Species	Silver Compound	Route	Dose (mg/kg/day)	% of Dose Cleared at 2 Days
Mouse	$^{110m}AgNO_3$	Oral	0.0011	99.61
		Intravenous	0.0010	82.08
Rat	$^{110m}AgNO_3$	Oral	0.0002	98.35
		Intravenous	0.0002	70.73
Monkey	$^{110m}AgNO_3$	Oral	0.00001	94.35
		Intravenous	0.00001	44.08
Dog	$^{110m}AgNO_3$	Oral	0.000005	90.38
		Intravenous	0.000003	15.00

[a]Furchner et al. 1968.

Dose conversion: Specific Activity was 8.7 Ci/g Silver nitrate
8.7 Ci/g = 8.7 x 10^6 μCi/1 x 10^3 mg = 8700 μCi/mg
μCi/μCi/mg=mg; mg/kg/day=dose

Dose Calculation:

Mouse: oral: 0.25 μCi/wt=26.5g: 0.25/8700=2.87 x 10^{-5}/0.0265 = 0.0011 mg/kg/day
iv: 0.25 μCi/wt=27.4g: 0.25/8700=2.87x10^{-5}/0.0274 = 0.0010 mg/kg/day
Rat: oral: 0.5 μCi/wt=355g: 0.5/8700=0.0001/0.355=0.0002 mg/kg/day
iv: 0.5 μCi/wt=369g: 0.5/8700=0.0001/0.369=0.0002 mg/kg/day
Monkey:oral: 0.6 μCi/wt=6730g: 0.6/8700=0.0001/6.73=0.00001 mg/kg/day
iv: 0.6 μCi/wt=6880g: 0.6/8700=0.0001/6.88=0.00001 mg/kg/day
Dog: oral: 0.6 μCi/wt=13330g: 0.6/8700=0.0001/13.33=0.000005 mg/kg/day
iv: 0.4 μCi/wt=14400g: 0.4/8700=0.000046/14.40=0.000003 mg/kg/day

and reports of cases where individuals have accidentally swallowed solutions of silver nitrate show that both inhalation and ingestion may cause gastric discomfort as well.

Studies in humans and animals indicate that silver compounds are absorbed readily by the inhalation and oral routes and poorly by the dermal route, and are distributed widely throughout the body. Observations made during surgery on silver exposed individuals and histopathologic studies of animals exposed to silver compounds demonstrate that within certain tissues of the body (most notably liver, kidney, pancreas, skin, conjunctiva of the eyes, and, to a lesser degree, certain brain areas) silver is deposited in the form of granules visible with the light microscope. However, with the exception of one report of decreased activity in mice exposed to silver nitrate, and one report of enlarged hearts in rats exposed to silver nitrate or silver chloride, there is no evidence that suggests that the silver deposits might interfere with the normal functioning of these organs in humans.

Death. There is no information concerning death in humans following exposure to silver compounds by any route.

Data concerning death observed in animals following oral and dermal exposure to silver compounds suggest that levels of exposure would have to be quite high to cause death in humans. High levels of colloidal silver were observed to cause death in rats when administered in drinking water for acute and intermediate exposure durations. The cause of death was unknown. The corresponding daily oral dose for a 70-kg man based on the dose levels tested would be approximately 12 grams. Death caused by silver has not been observed to occur in humans or animals following dermal exposure to silver compounds, nor is it expected to occur.

Systemic Effects. Silver nitrate and/or silver oxide have been reported to cause upper and lower respiratory tract irritation in humans when inhaled. In one case, inhalation of an unknown amount and chemical form of silver during work with molten silver ingots produced respiratory failure the day after exposure (Forycki et al. 1983). Without treatment the worker may have died. However, exposures such as this are not expected to be common and should be examined on a case by case basis.

Upper respiratory irritation has been observed in humans at estimated exposure levels of between 0.039 and 0.378 mg silver/m^3 for less than 1 to greater than 10 years. Evidence that silver colloid can act as an irritant is provided by the fact that ultrastructural damage was seen in the tracheal epithelium of rabbits following inhalation exposure to an unknown concentration of silver colloid. However, these effects are likely to be related to the caustic properties of the compounds, not to the presence of silver. The effects are not expected to persist when exposure to air containing silver compounds has stopped.

The same exposure conditions can also cause gastric discomfort in humans. Again, this effect is likely to be caused by the caustic effects of the silver compounds, and not the presence of silver. There is no evidence that suggests that dermal exposure to silver can cause gastric effects.

Occupational exposure to silver compounds has not been observed to affect blood counts. Although no supportive studies were located regarding hematological effects in other species or by other routes, the occupational exposure findings suggest that hematological effects are not a sensitive indicator of silver toxicity.

Silver is deposited in the glomerular basement membrane of the kidney of animals, and therefore might be expected to affect renal function. However, no studies of renal function in animals were located, and occupational studies in humans are not adequate for establishing a clear relationship between exposure to silver and renal impairment.

No human studies were located that indicate that exposure to silver or silver compounds will affect the cardiovascular system. However, an animal study did show an increase in the relative size of the left ventricle of rats that had been chronically exposed to silver nitrate or silver chloride in drinking water. Despite the suggestion by the authors that the increase in left ventricle size may be caused by vascular hypertension, ‘this effect has not been observed in animals or in humans. These endpoints have not been specifically addressed in reliable studies to date.

The predominant effect of exposure to silver in humans is the development of a characteristic, irreversible pigmentation of the skin. This condition is called argyria. Clinicians describe the pigmentation as slate-gray, bluegray, or gray in color and report it as most noticeable in areas of skin exposed to light. The pigmentation is not a toxic effect per se, nor is it known to be diagnostic of any other toxic effect. However, the change in skin color can be severe enough to be considered a cosmetic disfigurement in some cases.

The discoloring is likely to be caused by the photoreduction of silver chloride and/or silver phosphate in the skin. X-ray dispersive analysis of skin and other tissues reveals that the granules consist of silver complexed with sulfur and/or selenium. The photoreduced deposits are not removed by the body, and there are no clinical means of removing them.

Levels of silver exposure that have led to argyria in humans in the past are poorly documented, and it is not possible to establish minimum risk levels for this effect based on these data. Hill and Pillsbury (1939) in their review of cases of argyria report that total doses of silver that have resulted in argyria can be as low as a total of 1.4 grams of silver (as silver nitrate) ingested in small unspecified doses over several months.

An animal model for studying the pigmentation changes seen in humans does not exist. Therefore existing experimental animal data are of limited use in predicting the exposure levels that would result in argyria in humans. Granular deposits that contain silver have been observed in both pigmented and unpigmented skin of silver-exposed humans. Similar granules have been observed in various tissues in animals following silver exposure (see Section 2.2 and below). However, a direct correlation has not been established between the granular deposits seen in animals following exposure to silver and the deposition leading to skin discoloration in humans.

Immunological Effects. No studies were located that investigated toxic effects on the immune system in humans or animals exposed to silver, or that indicate that immune-related disease can be affected by silver exposure. Silver has been observed to elicit a mild allergic response (contact dermatitis) in humans following dermal exposure to various silver compounds.

Neurological Effects. Neurological effects attributable to silver have not been reported in humans nor have existing case or occupational studies focused on this endpoint. Exposure to silver has been observed to result in the deposit of silver in neurons of the central nervous system of a woman who had used nasal drops containing silver nitrate and in animals exposed by intraperitoneal injection and through drinking water. However, this effect is not known to be toxic. As measured using a controlled, blind assay, the activity of mice with silver deposits in their brain was less than that of controls. The decrease in activity could be attributable to other factors unrelated to central nervous system function (such as loss of appetite due to gastric effects, or general malaise) and the relevance to humans is not known.

Exposure to silver has been observed to affect the volume of hippocampal cell groups within the brain of animals. Several cell groups within the hippocampus (a well defined structure of the brain involved in some aspects of memory) are reduced in overall volume in rats exposed during their first 4 weeks of life to subcutaneously injected silver lactate (0.137 mg silver/kg/day) (Rungby et al. 1987). Unfortunately, the study is limited in that only one small region of the brain was examined. It is prudent to assume that similar effects would be observed in humans; however, the implications of the altered volume of these cell groups are not known.

Developmental Effects. Based on the existing information, it is not known whether silver causes developmental toxicity in humans. No studies were found concerning developmental effects in humans after exposure to silver. However, a human study by Robkin et al. (1973) did investigate the possibility of a relationship between the concentration of this heavy metal in the tissue of fetuses and the occurrence of developmental abnormalities. These authors reported that the concentration of silver in the fetal liver of 12 anencephalic human fetuses was higher (0.75±0.15 mg/kg) than the values from 12 fetuses obtained either through therapeutic abortions

(0.23±0.05 mg/kg), or in 14 spontaneously aborted fetuses (0.21±0.05 mg/kg). The concentration in 9 premature infants was 0.68±0.22 mg/kg. The authors could not determine if the higher concentrations of silver in anencephalic fetuses were associated with the malformation, or with fetal age.

Silver has been demonstrated in the brains of neonatal rats whose mothers received injections of silver lactate on days 18 and 19 of gestation (Rungby and Danscher 1984). As mentioned above, treatment of neonatal rats has also been found to reduce the volumes of certain cell groups within the hippocampus (Rungby et al. 1987). However, functional tests were not performed on these rats, and therefore, neither the significance of the silver accumulation, nor the decrease in regional hippocampal volume can be determined.

Reproductive Effects. The existing evidence does not point to a strong effect of silver on reproduction. However, no multigeneration reproductive studies were located, and therefore a firm conclusion regarding reproductive toxicity can not be made.

There is no historical evidence in humans to suggest that silver affects reproduction, although studies specifically designed to address this endpoint in humans were not located. One study in five male rats found that single subcutaneous injections of 0..04 millimole/kg silver nitrate caused temporary histopathological damage to testicular tissue (Hoey 1966). Eighteen hours after a single injection, silver caused shrinkage, edema, and deformation of the epididymal tubules. All affected tissues showed gradual recovery from damage following the initial injection, in spite of continued daily injections. Although treatment over a 30-day period had no effect on spermatogenesis, spermatozoa were observed with separated and pyknotic heads. A separate drinking water study in male rats did not observe changes in spermatozoa or diminution in fertility.

Finally, direct intrauterine injection of silver nitrate terminated pregnancies in monkeys (Dubin et al. 1981). Single dose intrauterine injections of 1% silver nitrate solution (0.78 mg/kg) resulted in vaginal bleeding for 1 or 2 days following treatment. The bleeding lasted for an average of 5.3 days. Pregnancy was terminated in all these cases. In subsequent pregnancies, these monkeys produced normal offspring. The relevance of direct uterine injection to human exposure conditions from NPL site contamination must be evaluated on a case by case basis since this effect has not been studied by the more common exposure pathways.

Genotoxic Effects. No studies were located that examined the mutagenicity or genotoxicity of silver in human cells in vivo or in vitro. Existing data on mutagenicity are inconsistent, but data on genotoxicity suggest that the silver ion is genotoxic. Table 2-6 presents the results of in vitro genotoxicity studies using bacteria and nonhuman mammalian cell cultures. From these studies and others it is evident that the silver ion

does bind with DNA in solution in vitro, and that it can interact with DNA in ways that cause DNA strand breaks and affect the fidelity of DNA replication (Goff and Powers 1975; Loeb et al. 1977; Luk et al. 1975; Mauss et el. 1980; Robison et al. 1982; Scicchitano and Pegg 1987). However, silver has not been found to be mutagenic in bacteria (Demerec et al. 1951; Kanematsu et al. 1980; McCoy and Rosenkranz 1978; Nishioka 1975; Rossman and Molina 1986).

Cancer. No studies were located regarding cancer in humans following inhalation, oral, or dermal exposure to silver or silver compounds. Fibrosarcomas have been induced in rats following subcutaneous imbedding of silver foil (Oppenheimer et al. 1956). In this study, imbedded silver metal foils appeared to produce fibrosarcomas earlier (latent period as short as 275 days compared to 364-714 days) and more frequently (32% of implantation sites compared to O-S%) than other metal foils (steel, tantalum, tin, and vitallium) tested. However, experiments on several metals (steel, tantalum, and vitallium) were not complete at the time of publication so adequate comparisons could not be made. In addition, it should be noted that several material are known to regularly produce such tumors when implanted subcutaneously in animals, and the relevance to carcinogenesis in humans is uncertain (Coffin and Palekar 1985). Both positive (Schmahl and Steinhoff 1960) and negative (Furst and Schlauder 1977) results for tumorigenesis have been reported following subcutaneous and intramuscular injection, respectively, of colloidal silver in rats. However, the relevance of these routes of exposure to exposure conditions at hazardous waste sites has not been clearly established. Animal toxicity and human occupational studies using normal routes of exposure have not provided indications of carcinogenicity, and silver is not expected to be carcinogenic in humans.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be

TABLE 2-6. Genotoxicity of Silver In Vitro

End Point	Species (Test System)	Results: With Activation	Results: Without Activation	Reference
Prokaryotic organisms:				
Gene mutation	Escherichia coli	ND	-	Demerec et al. 1951
	Salmonella typhimurium (strains TA1535, 1537, 1538, and 100)	-	-	McCoy and Rosenkranz 1978
	E. coli (enhancement of UV-light induced mutagenesis)	ND	-	Rossman and Molina 1986
	E. coli	ND	-	Kanematsu et al. 1980
	E. coli	ND	-	Nishioka 1975
	Photobacterium fischeri	ND	(+)	Ulitzur and Barak 1988
Eukaryotic organisms:				
DNA damage	Chinese hamster ovary cells (DNA strand breaks)	ND	+	Robinson et al. 1982
Viral transformation	Syrian hamster embryo	ND	+	Casto et al. 1979
DNA effects:				
Replication fidelity	Synthetic DNA	ND	+	Loeb et al. 1977

ND = no data; - = negative; (+) = weakly positive; + = positive.

taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc and selenium). Biomarkers of exposure to silver are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by silver are discussed in Section 2.5.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility e xist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify or Quantify Exposure to Silver

Silver can be detected in blood, urine, feces, hair, and biopsy specimens using standard analytic techniques, as well as whole body analysis using in vivo neutron activation. The presence of silver in these samples can be used, with varying degrees of accuracy depending on the sample, as a biomarker of exposure to silver compounds. Analysis of hair has been used to monitor for silver exposure (DiVincenzo et al. 1985). However, silver can be adsorbed onto hair surfaces as well as deposited during hair formation, and since current testing procedures cannot differentiate between the two modes, hair monitoring is an unreliable biomarker of exposure (DiVincenzo et al. 1985). Levels of silver in feces, blood, and urine have been associated with recent exposure via inhalation, oral, and dermal routes. Levels in these biological media may serve as more reliable, primary biomarkers of exposure to silver than levels in hair (DiVincenzo et al. 1985; Rosenman et al. 1979, 1987). These biomarkers appear to be independent of the route of exposure, but have not been quantitatively correlated with level and duration of exposure. The prevalence and estimated magnitude of silver deposition in the skin, however, were associated with duration of occupational exposure.

Because silver is eliminated primarily through the feces, recent exposure is most easily monitored through fecal analysis. Measurements of silver in the blood are also significant and indicate exposure to the metal. However,

silver is not always detected in the urine samples of workers with known exposure to the chemical, and is not as reliable a biomarker as feces and blood. DiVincenzo et al. (1985), for example, detected silver in 100% of feces samples and only 6% of urine samples from workers chronically exposed to silver compounds in air. Increased blood silver levels, above the detection limit for silver (0.6 μg/l00 mL blood), have been associated with inhalation exposure to the metal in a study by Rosenman et al. (1979).

Levels in biopsy specimens (e.g., of skin) provide information concerning repeated exposure (Blumberg and Carey 1934; East et al. 1980). After a burn victim had been dermally exposed to silver nitrate (as a bactericidal agent), Bader (1966) found silver primarily in the patient's skin as well as in the blood and urine. Further information can be found in Section 2.3.

2.5.2 Biomarkers Used to Characterize Effects Caused by Silver

Several effects associated with silver exposure have been reported in humans which may be useful as biomarkers of effects. The significance of these biomarkers, however, is in doubt, because they do not appear consistently in exposed individuals and do not seem to correlate well with levels and duration of exposure.

One easily observed effect of silver exposure is argyria which is a slate-gray or blue-gray discoloration of the conjunctivae, cornea, skin, and other epithelial surfaces. Oral, inhalation, or dermal absorption of silver may cause argyria in humans. A potential biomarker of silver deposition that could lead to this effect would be the presence of insoluble silver salts (e.g., silver chloride, sulfide, or phosphate) in skin biopsy, especially that associated with basement membrane (Danscher 1981). The granular deposition of silver in the cornea of workers has been loosely associated with complaints of decreas.ed night vision (Moss et al. 1979; Rosenman et al. 1979). However, Pifer et al. (1989) studied various ophthalmological end points in workers exposed to silver and silver compounds and could find no significant ocular impairments associated with the metal.

Low oxygen content in capillary blood, scattered thickening of lungs (as observed in chest radiograms), and upper respiratory irritation have been observed in studies of workers exposed intensely or chronically to molten silver or silver dusts (Forycki et al. 1983; Rosenman et al. 1979, 1987). Inhalation exposure also led to decreased red blood cell count and an increased mean corpuscular volume (Pifer et al. 1989). However, these potential hematologic biomarkers are not specific for silver exposure, and do not indicate or predict significant clinical sequelae.

Rosenman et al. (1987) found that inhalation exposure to silver caused changes in two renal end points which could be biomarkers of mild nephrotoxicity. In this study exposed workers exhibited lower creatinine clearance and higher excretion of the urinary enzyme N-acetyl-β-D

glucoseaminidase. However, workers in the study were also exposed to cadmium, a known nephrotoxic agent, which may have been responsible for the observed changes. Therefore, these biochemical effects cannot be considered reliable biomarkers of silver exposure. Occupational exposure to silver nitrate and silver oxide, leading to blood silver levels above 0.6 μg/100 mL, correlated strongly with increased complaints of abdominal pain (Rosenman et al. 1979). Moreover, dermal exposure to silver and silver compounds has been associated with a mild allergic reaction in humans which may be a biomarker of immunological effects (Catsakis and Sulica 1978; Hey1 1979; Marks 1966). Please refer to Section 2.2 of Chapter 2 for a more detailed discussion of the effects caused by silver and its compounds.

2.6 INTERACTIONS WITH OTHER CHEMICALS

As with other metals, relationships exist through which silver can influence the absorption, distribution, and excretion of one or more other metals. These influences are not known to increase the toxicity of other metals, nor are other metals known to add to any toxic effects of silver.

However, high intake of selenium (e.g., as sodium selenite or selenium oxide) may lead to increased deposition of insoluble silver salts in body tissues through the formation of silver selenide (Alexander and Aaseth 1981; Berry and Galle 1982; Nuttall 1987). Exposure to silver nitrate in drinking water concurrent with intraperitoneal injections of selenium dioxide results in a higher rate of deposition of granular deposits in the kidneys of rats than that seen with exposure to silver nitrate alone (Berry and Galle 1982). Higher deposition rates are likely to accelerate the development of argyria, although no data were located to confirm this.

No other studies were located regarding additive or synergistic toxic interactions of silver with any other substance. However, exposure to moderate-to-high silver levels (130-1000 ppm) in rats with dietary deficiencies such as vitamin E alone (Bunyan et al. 1968; Grass0 et al. 1969) or vitamin E and selenium (Van Vleet 1976; Van Vleet et al. 1981) can cause moderate-to-severe liver necrosis.

It should be noted that selenium plays a dual role in the toxicity of silver. On the one hand, it increases the silver deposition rate in body tissues, which suggests that humans exposed to both high selenium and high silver may be more likely to develop argyria. On the other hand, a seleniumdeficient diet combined with high silver intake can cause liver necrosis.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Populations that are unusually susceptible to toxic effects of silver exposure are those that have a dietary deficiency of vitamin E or selenium, or that may have a genetically based deficiency in the metabolism of these essential nutrients. Individuals with damaged livers may also be more

susceptible to the effects of silver exposure. In addition, populations with high exposures to selenium may be more likely to develop argyria. Furthermore, some individuals may exhibit an allergic response to silver.

2.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silver is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silver.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.8.1 Existing Information on Health Effects of Silver

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to silver are summarized in Figure 2-2. The purpose of this figure is to illustrate the existing information concerning the health effects of silver. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

The majority of literature reviewed concerning the health effects of silver in humans described case reports of individuals who developed argyria following oral exposure to silver. Occupational studies describing two separate worker populations were also located. The predominant route of exposure in the occupational studies is believed to have been inhalation, but the possibility of some degree of oral or dermal exposure cannot be ruled out. Information on human exposure is limited in that the possibility of concurrent exposure to other toxic substances cannot be excluded, and the duration and level of exposure to silver generally cannot be quantitated from the information presented in these reports.

As can be seen in Figure 2-2, very little information exists on the effects of dermal or inhalation exposure to silver in animals. Despite the need to evaluate NPL site exposure on a case by case basis, these routes are not expected to be significant sources of silver exposure. Furthermore, the oral exposure route has been examined primarily in regards to silver

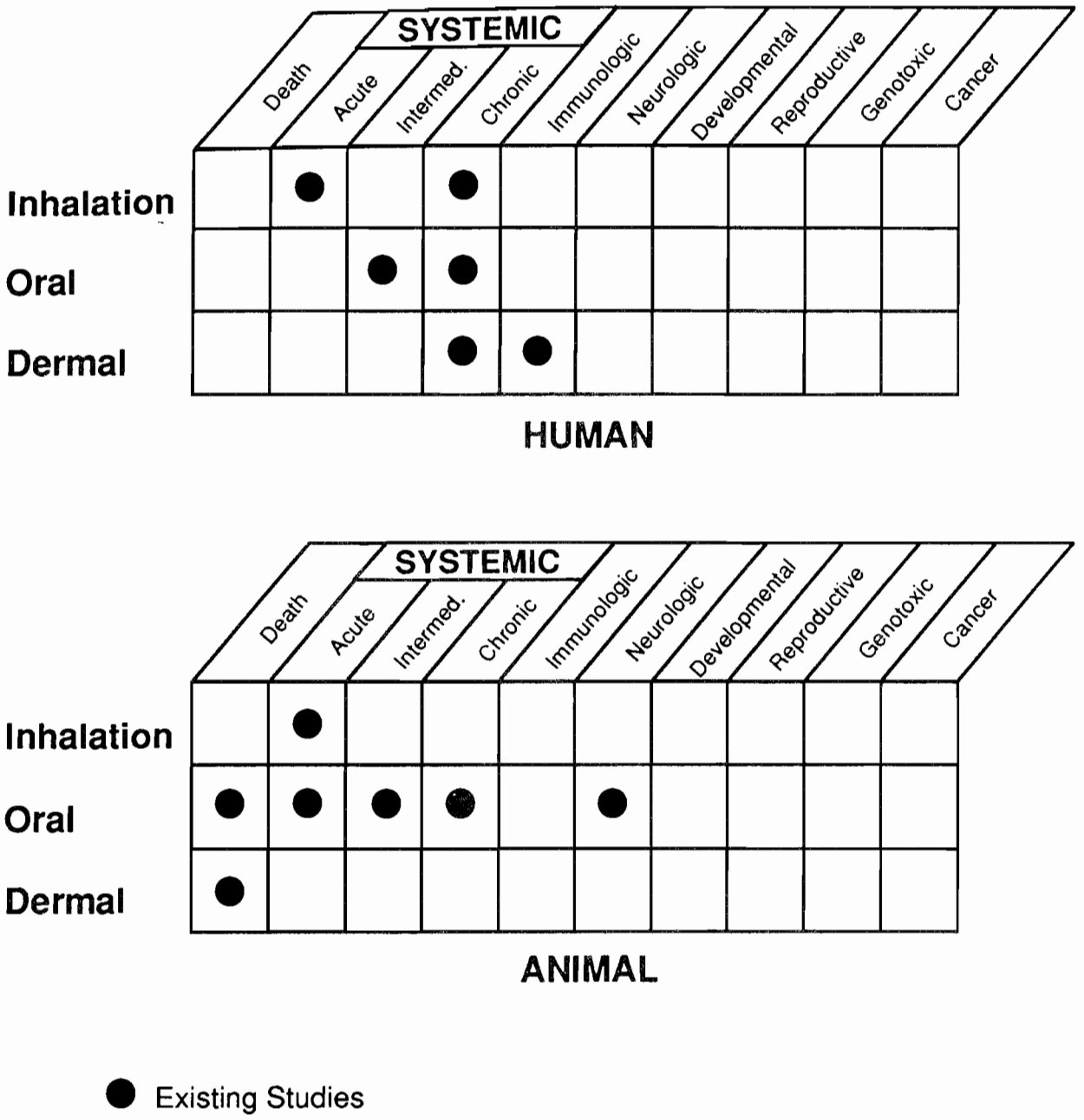

FIGURE 2-2. Existing Information on Health Effects of Silver

deposition in various tissues. The studies were not designed to examine other end points.

2.8.2 Identification of Data Needs

Acute-Duration Exposure. Information exists on the effects of acuteduration inhalation exposures to silver in humans and experimental animals. The information located is limited to one case report and an animal study that examined a single end point. Information concerning acute-duration exposure by the oral and dermal routes was not located. Insufficient data exist to establish a target organ or an MRL. Pharmacokinetic data that would support the identification of target organs across routes for acute-duration exposures were also not located. A more general data need is a comparative analysis of the toxicity of various silver compounds. Comparative toxicity data of silver compounds would allow a more accurate analysis of variations in toxicity caused by site-specific conditions, as may occur at NPL sites, or oxidizing and reducing conditions associated with specific exposure routes. Acuteduration exposure information would be useful because there may be populations adjacent to hazardous waste sites that might be exposed to silver for brief periods.

Intermediate-Duration Exposure. Information exists on the effects of intermediate dose exposures in both humans (inhalation and oral) and experimental animals (oral only). However, sufficient data do not exist to identify a target organ or establish an MRL for intermediate exposure durations. The exact duration and level of exposure in the human studies generally cannot be quantitated because the information is derived from anecdotal case reports rather than controlled epidemiological studies. Moreover, the animal studies predominantly describe deposition in the nervous system, eyes, and skin. One animal study has implicated the heart as a target organ. Controlled epidemiological studies in which exposure duration and level are quantified could be useful in identifying target organs in humans and for estimating the risk associated with intermediate-duration exposures. Additional animal studies investigating possible functional changes in organs in which silver deposition has been observed could also be used to identify possible health effects in humans. Animal studies that report deposition of silver in the skin employ intermediate or chronic exposure levels that are well above those estimated to cause argyria in humans. A reliable animal model of silver deposition rates and the occurrence of argyria may not be possible because of the photoreduction role that light plays.and the difficulty in providing similar conditions for laboratory animals. However, a dose-response study in which the deposition of silver in the skin is examined would be helpful in deriving MRLs for the development of argyria. Pharmacokinetic data that would support the identification of target organs across routes for intermediate-duration exposures were also not located. Little or no reliable information exists for other end points. Intermediateduration exposure information would be useful because there may be mobile or

migratory populations adjacent to hazardous waste sites that might be exposed to silver for similar durations.

Chronic-Duration Exposure and Cancer. No controlled epidemiological studies have been conducted in humans. Although argyria has been known to occur following chronic silver exposure, the general lack of quantitative information concerning this effect in humans or animals precludes the derivation of an MRL for this duration. Occupational studies weakly suggest that impairment of vision, gastrointestinal distress, or renal histopathology may result from chronic exposure to silver in humans. Additional information would be useful in confirming or denying these possibilities, and in establishing an MRL for chronic exposure. Pharmacokinetic data that would be useful in the identification of target organs or carcinogenic potential across routes for chronic duration exposures were also not located. Predominantly negative genotoxicity studies and the lack of reports of cancer associated with silver in humans, despite long-standing and varied usage, suggest that silver does not cause cancer. However, no chronic toxicity/carcinogenicity bioassays have been conducted in animals, and one study has reported an increase in tumors in rats following subcutaneous injections (the tumors occurred predominantly at the site of injection). A combined chronic toxicity/carcinogenicity study would be useful to address uncertainties in the database. Chronic-duration exposure information would be useful because there may be populations adjacent to hazardous waste sites that might be exposed to silver for long periods of time.

Genotoxicity. No studies were located that address the genotoxic effects of silver in humans. All information on silver genotoxicity comes from in vitro studies (predominantly microbial assays). These studies indicate that, while silver ions do interact with DNA in vitro, silver is not mutagenic. However, there is evidence that silver can cause DNA strand breaks and influence the fidelity of DNA replication. Better characterization of this evidence of genotoxicity, especially in in vivo test systems, would assist in the evaluation of silver genotoxicity.

Reproductive Toxicity. No information on the reproductive effects of silver in humans was located. Limited information in one study in laboratory animals suggests that chronic oral exposure to levels of silver high enough to cause widespread granular deposition has a low potential to induce adverse reproductive effects in either sex. However, this study did not examine all relevant reproductive end points. Furthermore, no studies were located that examined reproductive effects following silver exposure by inhalation or dermal routes. One subcutaneous injection study in animals demonstrated an effect on testicular tissue and sperm morphology (Hoey 1966). Examination of reproductive pathology in a go-day study would be useful to determine whether or not a multigeneration reproductive study is warranted to clarify the issue of reproductive effects of silver.

Developmental Toxicity. No information concerning developmental effects of silver in humans resulting from ingestion, inhalation, or dermal contact with silver was found. One study did investigate the relationship between silver levels in fetal tissue and the occurrence of deformities. However, a causal relationship was not established between exposure to silver and the deformities. Limited data in neonatal rats indicate that silver in drinking water can reduce the volume of certain well-defined brain regions. However, the functional significance of changes in volume of these small brain areas is not known. Data from pharmacokinetic studies that would support cross-route extrapolation were not located. Studies that further investigate the above end points for all routes of exposure would be useful to characterize the developmental effects of silver.

Immunotoxicity. Information on immunological effects of silver in humans is limited to clinical observations of allergic reactions to silver compounds after repeated dermal exposure in humans. No animal studies were located that examine immunologic end points, or that provide additional information regarding the allergic response to the silver ion. Information concerning the allergic potential of silver by the dermal, oral, and inhalation routes would be useful in identifying potential sensitive populations. A battery of immune function tests (e.g., ratio of T cells to B lymphocytes, levels of antibody classes, macrophage function, etc.) would be useful to determine whether silver compounds adversely affect the immune system.

Neurotoxicity. Existing studies show that silver can be deposited in anatomically defined regions of the brain .in both humans and animals following repeated oral exposure to silver. Other studies indicate that neuroanatomical changes can occur in young rats, and that the general activity level of exposed mice is less than that of unexposed mice. The significance of the neuroanatomical changes is not clear, and the study investigated only one small area that was not reported as an area of high silver deposition. Studies of the neuroanatomical areas that concentrate silver, and more specific neurobehavioral tests, would assist in defining the neurotoxic potential of silver for all routes of exposure.

Epidemiological and Human Dosimetry Studies. Most of the existing information on the effects of silver in humans comes from cases of individuals diagnosed with argyria following the intentional ingestion of medicinal silver compounds (silver nitrate and silver acetate) and from exposure of small numbers of worker populations in chemical manufacturing industries. Inherent study limitations include unquantified exposure concentrations and durations, as well as possible concomitant exposure to other toxic substances. Wellcontrolled epidemiological studies of communities living in close proximity to areas where higher than background levels of silver have been detected in soil and surface and/or groundwater, such as might occur near hazardous waste sites, and occupationally exposed groups would help supply information needed to clarify speculation regarding human health effects caused by silver.

Biomarkers of Exposure and Effect. Silver can be detected in blood, urine, feces, hair, and skin biopsy specimens. The best indictor of recent exposure to silver or silver compounds is detection of silver levels in feces and blood. Intermediate as well as long-term exposures are best monitored by measuring silver in blood or skin biopsy specimens. Argyria, the change in skin color associated with silver exposure, is also an indicator of chronic exposure. No other biomarkers for silver have been developed. Development of alternative biomarkers capable of detecting early exposure to low levels of silver would be useful in determining the possible toxic effects of this metal.

The only biomarkers of effect that have been reliably associated with silver exposure are argyria and granular deposits in the dermis and eyes. These are normally observed only in cases of intermediate and long-term exposure. Some clinical symptoms (e.g., gastrointestinal distress and respiratory discomfort) have been loosely associated with exposure, but are not definitive for exposure. No good quantitative correlations have been drawn between body levels of silver and these observed effects. Development of additional biomarkers of effect, especially for short-term and low-level silver exposure would be useful in determining the potential of silver to cause health impairment or disease. More information on the body burden of individuals with argyria, including skin biopsies, would help clinicians determine the risk of argyria for individuals with a history of silver exposure. If exposure levels of silver can be shown to correlate with specific adverse health effects, it may be possible to determine quantitative relationships between changes in tissue and/or body levels of silver.

Absorption, Distribution, Metabolism, and Excretion. The database for inhalation and dermal absorption of silver compounds in humans consists primarily of qualitative evidence from occupational case studies. Limited quantitative information exists on the oral absorption of silver compounds in humans. Research into the quantitative absorption of various silver compounds following relevant exposure routes would be useful to better predict the potential for toxic responses to particular silver compounds in humans.

Additional research into the comparative absorption, distribution, metabolism, and excretion of different silver compounds would allow a more accurate determination of the effects of silver exposure under specific environmental conditions. The current database primarily provides information concerning silver nitrate. Certain compounds that may exist at hazardous waste sites, such as silver oxide, silver thiosulfate, silver chloride, silver phosphate, and silver sulfide, have not been studied.

Studies were located for oral and dermal absorption in animals, but are lacking for absorption from inhalation exposure. Additional animal data would be useful in predicting the rate and extent of the inhalation absorption of various silver compounds in humans.

The only information that exists regarding distribution of silver in humans comes from an accidental exposure to an unknown quantity of radiolabeled silver metal dust. The distribution of various silver compounds is known in animals following inhalation and intravenous exposure; only qualitative information exists for oral or dermal exposure. Quantitative data on the distribution of various silver compounds following oral and dermal exposure would be useful when predicting the distribution of silver following exposure to specific silver compounds in humans.

There are data to assess the metabolic fate of silver compounds in humans and animals. Additional studies may shed light on possible variation in susceptibility to silver-related toxic effects. Elucidating the mechanism by which silver exerts toxicity in mammalian cells would assist in evaluating how this affects the health of the whole organism.

The kinetics of the excretion of various silver compounds are well characterized in animals and limited human data exist for inhalation and oral exposure. Further study into (1) the underlying basis for observed species differences; (2) quantitation of the elimination of dermally absorbed silver compounds; and (3) the basis for observed interpersonal differences in tolerance would aid in identification of human subpopulations with varying susceptibilities to the toxic effects of silver.

Comparative Toxicokinetics. A limited number of studies exist regarding the comparative toxicokinetics of orally administered silver compounds in rats, dogs, monkeys, and humans. A more complete comparison of the absorption and elimination of silver in humans and rats may be warranted given that much of the toxicokinetic data comes from rats. It would also be useful to acquire data on the comparative toxicokinetics of various silver compounds in several species of experimental animals and in humans following inhalation and dermal exposure in order to model the kinetics of silver deposition across different exposure scenarios and within sensitive populations.

2.8.3 On-going Studies

No on-going studies were identified that explore the health effects or toxicokinetics of silver or that attempt to associate silver levels in human tissues with effects.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The synonyms and identification numbers for silver and selected silver compounds are listed in Tables 3-1 through 3-6.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of silver and selected silver compounds are given in Tables 3-7 through 3-12.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Silver

	Value	Reference
Chemical name	Silver	
Synonyms	Silver; argentum; argentum crede; *CI 77820*; shell silver; silver atom; silver colloidal; silflake; silpowder; silber	CHEMLINE 1988; *HSDB 1988*
Trade names	No data	
Chemical formula	Ag	Grayson 1983; Windholz 1983
Chemical structure	Ag	HSDB 1988
Wiswesser	• Ag	HSDB 1988
Identification numbers:		
CAS Registry	7440-22-4	HSDB 1988
NIOSH RTECS	VW 3500000	HSDB 1988
EPA Hazardous Waste	D011	HSDB 1988
OHM/TADS	7216881	HSDB 1988
DOT/UN/NA/IMCO shipping	No data	
HSDB	5034	HSDB 1988
NCI	No data	
STCC	No data	

HSDB = Hazardous Substance Data Bank; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Chemical Identity of Silver Nitrate

	Value	Reference
Chemical name	Silver nitrate	
Synonyms	Lunar caustic; fused silver nitrate; molded silver nitrate; argenti; nitras; nitric acid silver (I) salt; nitric acid silver (1+) salt; Silver (1+) nitrate	HSDB 1988; Weiss 1986; Windholz
Trade names	No data	
Chemical formula	$AgNO_3$	Grayson 1983; Weiss 1986
Chemical structure	$Ag^+ \ NO_3^-$	HSDB 1988
Wiswesser	AG N-03	HSDB 1988
Identification numbers:		
CAS Registry	7761-88-8	Grayson 1983; Weiss 1986
NIOSH RTECS	VW 4725000	HSDB 1988
EPA Hazardous Waste	No data	
OHM/TADS	7216883	HSDB 1988
DOT/UN/NA/IMCO shipping	DOT 1493 UN 1493 IMCO 5.1	Weiss 1986 HSDB 1988
HSDB	685	HSDB 1988
NCI	No data	
STCC	49 187 42	HSDB 1988

HSDB = Hazardous Substance Data Bank; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-3. Chemical Identity of Silver (I) Oxide

	Value	Reference
Chemical name	Silver (I) oxide	
Synonyms	Argentous oxide; silver (1+) oxide; disilver oxide; silver oxide	Windholz 1983
Trade names	No data	
Chemical formula	Ag_2O	Grayson 1983; Weiss 1986
Chemical structure	$Ag^+ \ O^{2-} \ Ag^+$	RTECS 1989
Wiswesser	AG 2-0	RTECS 1989
Identification numbers:		
CAS Registry	20667-12-3	Grayson 1983
NIOSH RTECS	VW 4900000	RTECS 1989
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	IMO/UN-not listed	Weiss 1986
HSDB	No data	
NCI	No data	
STCC	No data	

RTECS = Registry of Toxic Effects of Chemical Substances; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-4. Chemical Identity of Silver (II) Oxide

	Value	Reference
Chemical name	Silver (II) oxide	
Synonyms	Argentic oxide; silver peroxide; silver suboxide; divasil	Windholz 1983
Trade names	No data	
Chemical formula	AgO	Grayson 1983
Chemical structure	Ag^{2+} O^{2-}	Grayson 1983
Wiswesser	No data	
Identification numbers:		
CAS Registry	1301-96-8, 35366-11-1	Grayson 1983
NIOSH RTECS	No data	
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	
STCC	No data	

CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects and Chemical Registry; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-5. Chemical Identity of Silver Sulfide

	Value	Reference
Chemical name	Silver sulfide	
Synonyms	Acanthite; argentous sulfide	Weast 1988 Windholz 1983
Trade names	No data	
Chemical formula	Ag_2S	Grayson 1983
Chemical structure	Ag^+ S^{2-} Ag^+	Windholz 1983
Wiswesser	No data	
Identification numbers:		
CAS Registry	21548-73-2	Grayson 1983
NIOSH RTECS	No data	
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	
STCC	No data	

CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-6. Chemical Identity of Silver Chloride

	Value	Reference
Chemical name	Silver chloride	
Synonyms	Silver (I) chloride; Silver monochloride	RTECS 1988
Trade names	No data	
Chemical formula	AgCl	Grayson 1983
Chemical structure	Ag^+ Cl^-	RTECS 1988
Wiswesser	No data	
Identification numbers:		
CAS Registry	7783-90-6	Grayson 1983
NIOSH RTECS	VW 3563000	RTECS 1988
EPA Hazardous Waste	No data	
OHM/TADS	No data	
DOT/UN/NA/IMCO shipping	No data	
HSDB	No data	
NCI	No data	
STCC	No data	

RTECS = Registry of Toxic Effects of Chemical Substances; CAS = Chemical Abstracts Services; NIOSH = National Institute for Occupational Safety and Health; EPA = Environmental Protection Agency; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; and STCC = Standard Transport Commodity Code.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-7. Physical and Chemical Properties of Silver

	Value	Reference
Molecular weight	107.868	Weast 1988
Color	Lustrous, white	Weast 1988
Physical state	Solid metal	Grayson 1983
Valence state	+1,+2	Windholz 1983
Melting point	961.93°C	Weast 1988
Boiling point	2,212°C at 760 mmHg	Weast 1988
Density at 20°C	10.50 g/cm^3	Weast 1988
20°C	10.43 g/cm^3 (hard drawn)	Grayson 1983
20°C	10.49 g/cm^3 (annealed	Grayson 1983
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	Insoluble; soluble in nitric acid, not in sulfuric acid and alkali cyanide solutions	Windholz 1983; ITII 1982
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure:		
Liquid silver at 1,865°C	100 mmHg	Weast 1988
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	Dust is moderately flammable	ITII 1982
Conversion factors	Troy ounces x 31.1034768 = grams	Weast 1988

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-8. Physical and Chemical Properties of Silver Nitrate

	Value	Reference
Molecular weight	169.89	Weast 1988
Color	Colorless or white	Grayson 1983
Physical state	Solid crystalline	Weast 1988
Melting point	212°C	Grayson 1983
Boiling point	Decomposes at 440°C	Grayson 1983
Density at 19°C	4.35	HSDB 1988
at 19°C	4.33	Weiss 1986
Odor	Odorless	Weiss 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 0°C	122 g/100 mL H_2O at 0°C	HSDB 1988
Organic solvents	Soluble in ethanol and acetone	Grayson 1983
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	Not flammable	Weiss 1986
Flashpoint	Not flammable	Weiss 1986
Flammability limits	Not flammable	Weiss 1986

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-9. Physical and Chemical Properties of Silver (I) Oxide

	Value	Reference
Molecular weight	231.8	Weiss 1986
Color	Dark brown-to-black	Windholz 1983
Physical state	Solid crystalline	Weast 1988; Weiss 1986; Windholz 1983
Melting point	Decomposes at 230°C	Weast 1988
Boiling point	Decomposes between 200°-300°C	Windholz 1983
	Decomposition complete at 300°C	Grayson 1983
Density at 20°C	7.14 g/cm^3	Weiss 1986
Odor	Odorless	Weiss 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	$2.2x10^{-2}$ g/L	Grayson 1983
Organic solvents	Practically insoluble in alcohol	Windholz 1983
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	Not flammable	Weiss 1986
Flammability limits	Not flammable	Weiss 1986

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-10. Physical and Chemical Properties of Silver (II) Oxide

	Value	Reference
Molecular weight	123.88	Windholz 1983
Color	Charcoal gray powder, black crystal	Grayson 1983; Windholz 1983
Physical state	Solid	Windholz 1983
Melting point	No data	
Boiling point	Decomposes above 100°C	Windholz 1983
Density	No data	
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	Decomposes in aqueous solution	Windholz 1983
Organic solvents	No data	
Partition coefficients:	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-11. Physical and Chemical Properties of Silver Sulfide

	Value	Reference
Molecular weight	247.80	Weast 1988
Color	Gray-black	Weast 1988
Physical state	Solid	Grayson 1983
Melting point	No data	
Boiling point	Decomposes at 810°C	Grayson 1983
Density at 20°C	7.326 g/cm^3	Weast 1988
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	$1.4x10^{-4}$ g/L	Grayson 1983
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure	No data	
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-12. Physical and Chemical Properties of Silver Chloride

	Value	Reference
Molecular weight	143.34	Windholz 1983
Color	White	Windholz 1983
Physical state	Solid	Windholz 1983
Melting point	455°C	Windholz 1983
Boiling point	1,550°C	Windholz 1983
Density at 20°C	5.56 g/cm^3	Windholz 1983
Odor	No data	
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 25°C	1.93 mg/L	Windholz 1983
Organic solvents	No data	
Partition coefficients	No data	
Vapor pressure		
Henry's law constant	No data	
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	

4. PRODUCTION, IMPORT, USE AND DISPOSAL

4.1 PRODUCTION

Silver is a rare, but naturally occurring, element. It is often found deposited as a mineral ore in association with other elements. It is acquired primarily as a by-product during the retrieval of copper, lead, zinc, and gold ores (Grayson 1983). The primary silver mines of the United States are located in the Coeur d'Alene mining district in the northern Idaho panhandle (Smith and Carson 1977). This area accounts for approximately 71% of domestic mine production (Drake 1980). It is mined using either open pit or underground methods, and the ore is then upgraded through a series of processes including flotation and smelting. The silver is finally extracted electrolytically by the Moebius process, the Balbach-Thum process, or the Parkers process (Grayson 1983; Smith and Carson 1977).

World mine production in 1986 was 419.8 million troy ounces (for conversion: troy ounces x 31.1034768 = grams) (Reese 1986). Mine production in the United States declined from 1978 to 1986, reaching a low of 34.2 million troy ounces in 1986, due to a combination of falling silver prices and rising production costs (Reese 1986). This trend appeared to continue according to a survey conducted by The Silver Institute in 1988 and 1989. The United States production of silver from ores and concentrates was 3.4 and 4.2 million troy ounces in 1988 and 1989, respectively. However, when recovered silver is included in the production figures, total production was 8.8 and 9.3 million troy ounces for 1988 and 1989, respectively (The Silver Institute 1990). United States consumption in 1986 reached a high of 126.4 million troy ounces,-largely due to increased industrial consumption and use in special issue coinage (Reese 1986). In 1987, the estimated consumption was 63.7 million troy ounces for the United States and 172 million troy ounces worldwide (The Silver Institute 1988)

Since 1951, silver consumption has exceeded its extraction from ore. Secondary silver production involves the recovery of silver from new and old scrap, resulting from silver-containing wastes generated by industry and the consumer. Recycled silver accounted for 40% of U.S. refinery production in 1971 and had increased to 67% by 1974 (Smith and Carson 1977). It was estimated to be 61% and 56% in 1988 and 1989, respectively (The Silver Institute 1990). The estimated world-wide recovery of silver from the photographic industry is about 67% of the total used (The Silver Institute 1988). It has been estimated that 80%, 68%, and 75% of today's annual consumption by the electrical, industrial-alloy, and art industries, respectively, is recycled silver, but these estimates may be high.

4.2 IMPORT

The United States 1986 net import reliance approximated 60% of apparent domestic consumption. Despite this, the 1986 U.S. dependence on foreign imports decreased. Import levels fell from 152.6 million troy ounces in 1985 to 144.9 million troy ounces in 1986 (Reese 1986).

The largest decrease in imported silver was from the United Kingdom and Switzerland. For these two countries import levels fell by 18.1 million ounces, primarily in the form of refined bullion. A total of 125.4 million troy ounces of refined silver were imported in 1986 with only 9.5 million troy ounces accounted for in other forms.

U.S. exports of silver decreased slightly from 28.8 million troy ounces in 1985 to 25.1 million troy ounces in 1986 (Reese 1986).

4.3 USE

Silver metal and silver compounds have been and still are used in a wide variety of ways. In the past, silver was used for surgical prostheses and/or splints, fungicides (both of which are now obsolete), and coinage (discontinued from general circulation within the United States in 1970). Although silver still serves some of the above functions, the current uses are even more varied. Photographic materials accounted for 45% of the U.S. consumption in 1986. Electrical and electronic products, such as electrical contacts, silver paints, and batteries, consumed approximately 25%. Silver has been an important component in the manufacture of bearings in the past, although today its use in this area is limited by cost and availability. Silver is also an important component in brazing alloys and solders, which represent approximately 5% of the 1986 silver consumption. More aesthetic uses of silver include electroplated ware, sterling ware, and jewelry; in 1986, they accounted for 11% of recorded uses.

Other uses account for the remaining 14%; these include use in mirrors, dental amalgam, and medical supplies for treatment of burns, use as a catalyst in the manufacture of formaldehyde and ethylene oxide, as an active agent for purification and disinfection of drinking water and water in swimming pools, in certain chemical analyses involving titration, and in cloud seeding (Grayson 1983; HSDB 1988; NRC 1977; Smith and Carson 1977). Silver ions are also used medically as an antibacterial agent (Becker 1987; Becker et al.1978; Fox et al. 1969; Webster et al. 1981).

4.4 DISPOSAL

Treatment of air emissions containing silver is not a concern as atmospheric emissions rarely approach the federal threshold limit value for occupational exposure of 0.01 mg/m^3 (Smith and Carson 1977).

Moreover, as consumption of silver-containing products outweighs supply, these products tend to be recycled whenever feasible. The largest source of nonrecycled silver in the waste stream is attributable to photographic material use by small-scale consumers (Smith and Carson 1977). This tends to be released in the form of silver thiosulfate, which is converted into insoluble silver forms by micro-organisms during wastewater treatment (Grayson 1983). Several methods have been suggested for recovering silver from various waste media, including waste water, solid waste, and gas effluents. These include electrolytic recovery, agglomeration, and metal concentration (CHMR 1989). At present the criteria for land disposal practices are undergoing significant revision, and consultation with environmental regulatory agencies is advised (HSDB 1988).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Silver is a rare element, which occurs naturally in its pure form as a white, ductile metal, and in ores. It has an average abundance of about 0.1 ppm in the earth's crust and about 0.3 ppm in soils. There are four oxidation states (0, l+, 2+, and 3+); the 0 and 1+ forms are much more common than the 2+ and 3+ forms. Silver occurs primarily as sulfides, in association with iron (pyrite), lead (galena), and tellurides, and with gold. Silver is found in surface waters in various forms: (1) as the monovalent ion (e.g., sulphide, bicarbonate, or sulfate salts); (2) as part of more complex ions with chlorides and sulfates; and (3) adsorbed onto particulate matter.

Silver is released to air and water through natural processes such as the weathering of rocks and the erosion of soils. Important sources of atmospheric silver from human activities include the processing of ores, steel refining, cement manufacture, fossil fuel combustion, municipal waste incineration, and cloud seeding. The total U.S. annual release of silver to the environment as a result of human activities in 1978 was estimated to be approximately 2 million kg. ,Of this amount, 77% was from,land disposal of solid waste, 17% was discharged to surface waters, and 6% emitted to the atmosphere. Ore smelting and fossil fuel combustion emit fine particles of silver that may be transported long distances and deposited with precipitation. The major source of release to surface waters is effluent from photographic processing. Releases from the photographic industry and from disposal of sewage sludge and refuse are the major sources of soil contamination with silver. Sorption is the dominant process controlling partitioning in water and movement in soil. Silver may leach from soil into groundwater; acidic conditions and good drainage increase the leaching rate. Silver is bioconcentrated to a moderate extent in fish and invertebrates.

The general population is exposed to silver primarily through the ingestion of drinking water and food. The most recent estimate by NIOSH indicates that about 70,000 people are potentially exposed to silver in workplace environments in the United States. Inhalation is probably the most important route of occupational exposure. Populations with exposure to higher than background levels of silver include workers in industries processing or using the compound and members of the general public who consume drinking water or food containing elevated levels of silver. Sources of elevated dietary silver include seafood from areas near sewage outfalls or industrial sources and crops grown in areas with high ambient levels of silver in the air or soil.

According to the VIEW Database (1989), silver has been found at 27 sites on the National Priority List of 1,177 sites. The frequency of these sites

within the United States can be seen in Figure 5-l. EPA's Contract Laboratory Program (CLP) statistical database indicates that silver has been detected at 100% of the 2,783 Superfund hazardous waste sites that have had samples of all media analyzed by the CLP (CLP 1988).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

The total U.S. annual anthropogenic release of silver to the atmosphere from production processes and consumptive uses in 1978 was estimated at 77,700 kg (Scow et al. 1981). Of this amount, an estimated 30,000 kg were released from metals production, 22,000 kg from use in electrical contacts and conductors, 9,000 kg from coal and petroleum combustion, 7,000 kg from iron and steel production, 2,000 kg from cement manufacture, and the remainder from miscellaneous uses. Urban refuse was the source of an additional 10,000 kg. Smith and Carson (1977) estimated that cloud seeding with silver iodide contributed 3,100 kg annually (based on data from the early 1970s).

5.2.2 Water

The total U.S. annual release of silver to surface waters in 1978 from production processes and consumptive uses was estimated to be 125,000 kg (Scow et al. 1981). Of this amount, an estimated 65,000 kg were released from photographic developing, 54,000 kg from photographic manufacture, 5,000 kg from metals production, and the remainder from miscellaneous uses. An additional 70,000 kg were estimated to be released from sewage treatment plants, 72,000 kg from urban runoff, and 438,000 kg from natural sources (e.g., soil erosion). Silver released in precipitation as a result of cloud seeding has decreased and is not expected to contribute significant amounts to water (Scow et al. 1981). Leachates containing silver may enter ground waters when tailing ponds or piles are situated in areas with high water tables or when abandoned mines or sections of mines are saturated (Letkiewicz et al. 1984).

Other sources of silver release to surface waters include textile plant wastewater effluent (Rawlings and Samfield 1979); petroleum refinery effluents (Snider and Manning 1982); and quench water and fly ash scrubber water effluents from municipal incinerators (Law and Gordon 1979). Silver was detected in 7 of 58 (12%) samples from the National Urban Runoff Program survey (Cole et al. 1984).

5.2.3 Soil

The total U.S. annual release of silver to land from production processes and consumptive uses in 1978 was estimated at 1.01 million kg (Scow et al. 1981). Of this amount, an estimated 630,000 kg were released from the photographic industry (in manufacture and developing), 165,000 kg from metals

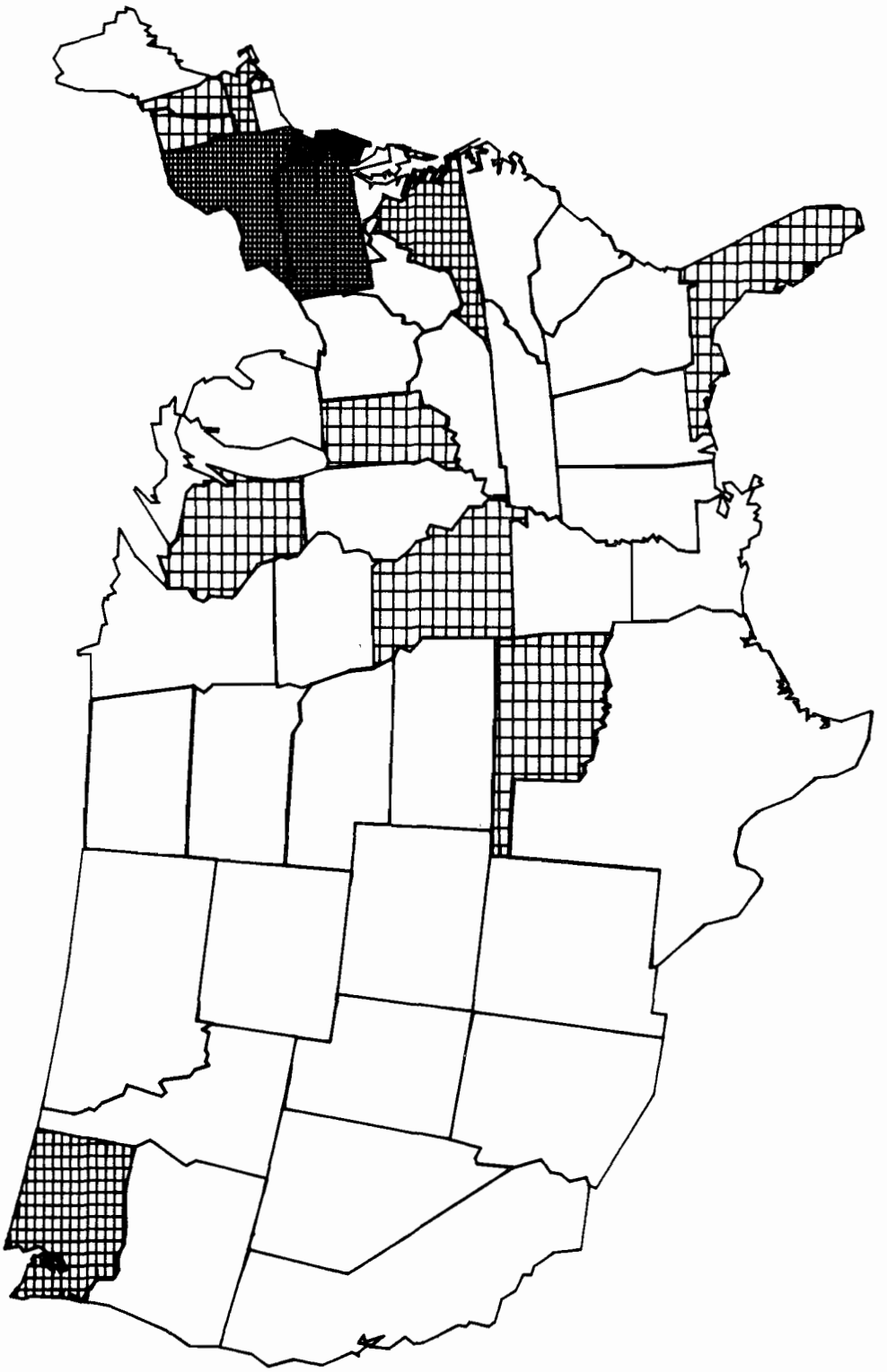

FIGURE 5-1. FREQUENCY OF SITES WITH SILVER CONTAMINATION

production, 150,000 kg from uses in electrical contacts and conductors, 60,000 kg from uses in brazing alloys and solders, and the remainder from miscellaneous uses. An additional 370,000 to 520,000 kg were estimated to be released from urban refuse and 220,000 kg from sewage treatment. Smith and Carson (1977) estimated that the use of silver containing photographic materials contributed an annual 370,000 kg in sewage sludge; of this amount an estimated 52.5% was placed in landfills, 26.7% was lagooned, and 20.8% was spread on land.

The major source of elevated silver levels in cultivated soils is from the application of sewage sludge and sludge effluents as agricultural amendments. Additional anthropogenic sources of silver in soil include atmospheric deposition (especially from ore processing); landfilling of household refuse, sewage sludge, or industrial wastes; and leaching of metal tailings (Smith and Carson 1977).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The global biogeochemical movements of silver are characterized by releases to the atmosphere, water, and land by natural and man-made sources, possible long-range transport of fine particles in the atmosphere, wet and dry deposition, and sorption to soil and sediments. The major forms of silver in the atmosphere are probably metallic silver, silver sulfide, silver sulfate, silver carbonate, and silver halides (Smith and Carson 1977). Silver is released to the atmosphere as an aerosol (suspension of solid or liquid particles in a gas such as air). Mining operations such as grinding emit large particles (more than 20 μ diameter) that settle near the source while particles emitted from smelting, fossil-fuel fired power plants, and solid waste incinerators are smaller and are likely to be transported away from the source of release (Scow et al. 1981). Fine particles (less than 20 μ diameter) in the aerosol tend to be transported long distances in the atmosphere and are deposited with precipitation. Long-range atmospheric transport of silver is indicated by several studies in which atmospheric particulate concentrations were elevated above background levels in areas removed from cloud seeding or mining activities (Davidson et al. 1985; Struempler 1975). Scow et al. (1981) estimated that about 50% of the silver released into the atmosphere from industrial operations will be transported more than 100 km and will eventually be deposited by precipitation.

The transport and partitioning of silver in surface waters and soils is influenced by the particular form of the compound. Lindsay and Sadiq (1979) stated that under oxidizing conditions the primary silver compounds would be bromides, chlorides, and iodides, while under reducing conditions the free metal and silver sulfide would predominate. In water, the major forms of silver are as the monovalent ion in the form of sulfate, bicarbonate, or sulfate salts; as part of more complex ions with chlorides and sulfates; and

as an integral part of, or adsorbed onto, particulate matter (Boyle 1968). In one study, silver in river water was primarily found in the following forms: silver ion (Ag+) -- 53-71%, silver chloride (Ag Cl°) -- 28-45%, silver chloride ion ($AgCl_2^-$) -- 0.6-2.0% (Whitlow and Rice 1985). Callahan et al. (1979) stated that sorption is the dominant process leading to the partitioning of silver in sediments. Significant quantities of silver in water are sorbed by manganese dioxide; pH and oxidation-reduction conditions affect sorption (Anderson et al. 1973). Kharkar et al. (1968) reported that approximately 90% of the silver in rivers was in a dissolved form and 10% was a suspended solid. Concentrations in lake sediments were reported to be 1000 times that of the overlying waters; the highest content was associated with fine-grained sediments (Freeman 1977).

The mobility of silver in soils is affected by drainage (silver tends to be removed from well-drained soils); oxidation-reduction potential and pH conditions (which determine the reactivity of iron and manganese complexes which tend to immobilize silver); and the presence of organic matter (which complexes with silver and reduces its mobility) (Boyle 1968). The distribution coefficient (Kd: ratio of the concentration in soil to the concentration in water) for silver in a number of soils ranged from 10 to 1,000 (Baes and Sharp 1983). Factors that affect the Kd include soil pH, clay content and particle size distribution, organic matter content, and free iron and manganese oxide content. The enhanced ability of organic matter to immobilize silver is demonstrated by the increased levels of silver found in peat and bog soils and in marshes (Boyle 1968). In pasture plants growing in the vicinity of an airborne source of silver such as a smelter, silver in the leaves is apparently derived from deposition ,of airborne silver, while concentrations in the roots are from soil uptake (Ward et al. 1979). Silver levels in the leaves were slightly greater than levels in the roots.

Silver accumulation in marine algae appears to result from adsorption rather than uptake; bioconcentration factors of 13,000-66,000 have been reported (Fisher et al. 1984).

Data on the potential for accumulation of silver has been studied in several aquatic species. Several of these studies do not conform to current bioconcentration test procedures in terms of numbers of fish, duration of exposure, and measurement of concentrations in aquaria. EPA (1980a) reported a bioconcentration factor of less than 1 in bluegills (Lepomis macrochirus) exposed to silver nitrate for 28 days. Approximate bioaccumulation factors of 4-6 for bluegill were calculated based on a 6-month study and 2-10 for large mouth bass (Micropterus salmoides) exposed to silver nitrate for 4 months (both dry weight) (Coleman and Cearley 1974).

Terhaar et al. (1977) studied bioconcentration (uptake from water) and bioaccumulation (uptake from food and water) of silver thiosulfate complexes in algae (Scenedesmus sp.), water flea (Daphnia magna), mussels (Ligumia sp. and Margaritifera sp.), and fathead minnow (Pimephales promelas) in 10-week

exposures. Bioconcentration indices were 96-150 for algae, 12.2-26 for Daphnia, 5.9-8.5 for mussels, and 1.8-28 for fish. Bioaccumulation indices were 9-26 for Daphnia, 6.6-9.8 for mussels, and 4.0-6.2 for fish. These indices, which are based on measured wet weight concentrations in biota and nominal concentrations in water, indicate little potential for silver biomagnification (systematic increase in residue concentrations moving up a food chain) in the tested aquatic food chain.

Bioconcentration factors of 1,055-7,650 (wet weight) were estimated in a 21-month study with the mussel (Mytilus edulis) in salt water (Calabrese et al. 1984). The clam, Macoma balthica, contained silver at 32-133 μg/g (dry weight tissue) in an area of San Francisco Bay near a sewage outfall; background concentrations in this species in the bay were less than 1 μg/g (Thomson et al. 1984). These data indicate that inputs of silver to an estuary are available to sediment-dwelling animals. Silver from sewage sludge at an ocean disposal site was bioaccumulated by the sea scallop (Placopecten magellanicus). Maximum concentrations in scallops located near the disposal site were 9.08 ppm (dry weight tissue) while scallops located away from the site had levels less than 1 ppm (Pesch et al. 1977). The estimated biological half-lives for the elimination of silver were 26.4 days for the Pacific oyster (Crassostrea gigas) and 149.1 days for the American oyster (C. virginica) (Okazaki and Panietz 1981).

5.3.2 Transformation and Degradation

5.3.2.l Air

Particulates of metallic silver emitted from the burning of fossil fuels and municipal refuse are likely to become coated with silver oxide, silver sulfide, and silver carbonate as the particles cool and undergo deposition (Smith and Carson 1977).

5.3.2.2 Water

In fresh water, silver may form complex ions with chlorides, ammonium (in areas of maximum biological activity), and sulfates; form soluble organic compounds such as the acetate and the tartrate; become adsorbed onto humic complexes and suspended particulates; and become incorporated into, or adsorbed onto, aquatic biota (Boyle 1968). Where decaying animal and plant material are abundant, silver strongly precipitates as the sulfide or combines with humic materials (Smith and Carson 1977).

5.3.2.3 Soil

Silver tends to form complexes with inorganic chemicals and humic substances in soils (Boyle 1968). Since silver is toxic to soil microorganisms and inhibits bacterial enzymes (Domsch 1984), biotransformation is not expected to be a significant process.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Silver was measured in particulate samples from rural and urban areas both adjacent to and removed from activities such as metal smelting, refining, and silver iodide cloud seeding. Background levels appear to be less than 1 ng/m^3 as evidenced by the measurement of average silver concentrations of 0.018 ng/m^3 at Great Smoky Mountains National Park; 0.012 ng/m^3 at Olympic National Park; and less than 0.19 ng/m^3 at Glacier National Park (Davidson et al. 1975). The highest particulate levels (mean -- 10.5 ng/m^3; range -- 0.936-36.5 ng/m^3) were measured in Kellogg, Idaho (in the Coeur d'Alene River Basin) near a large smelter complex (Ragaini et al. 1977). In an industrialized area of northwest Indiana, silver was measured at less than l-5 ng/m^3 (Harrison et al. 1971). A level of 1 ng/m^3 was reported by Douglas (1968) in a rural cloud-seeding target area. In a rural area of Nebraska where no cloud seeding was known to have occurred, Struempler (1975) found particulate silver concentrations averaged 0.04-0.15 ng/m^3 during three sampling periods. This researcher theorized that anthropogenic sources, such as long-range transport from cloud seeding, were responsible for the enrichment of silver by factors of 326-355 over its average concentration in the earth's crust. Silver concentrations in precipitation resulting from seeding clouds with silver iodide were 10-4500 ng/L compared with concentrations of 0-20 ng/L without cloud seeding (Cooper and Jolly 1970).

5.4.2 Water

Boyle (1968) reported average (background) ambient concentrations of silver in fresh waters of 0.2 μg/L and in sea water of 0.25 μg/L. Waters that leach silver-bearing deposits (e.g., in mining areas) may carry up to 100 times more silver than other fresh waters (Scow et al. 1981). Leaching is enhanced by low pH (Smith and Carson 1977). In samples of 170 lakes in California, silver concentrations averaged 0.1 μg/L with a maximum of 6.0 μg/L (Bradford et al. 1968). Kharkar et al. (1968) reported that the average silver concentration of 10 U.S. rivers was 0.30 μg/L (range: 0.092-0.55 μg/L). In another survey, Kopp (1969) found silver in 6.6% of 1,577 surface waters sampled with a mean detected concentration of 2.6 μg/L (range: 0.1-38 μg/L). For 1970-1979, according to U.S. surface water sampling data from EPA's STORET database, the annual mean levels ranged from 1 μg/L to 9 μg/L and annual maximum concentrations were 94 μg/L to 790 μg/L (Scow et al. 1981). In 10 out of 13 major U.S. river basins, silver concentrations decreased from 1975-1979 as compared with 1970-1974. Concentrations increased in the North Atlantic, Southeast, and Lower Mississippi basins. In the U.S. Geological Survey, Water Resources Division portion of the database (from the early 1960s to mid-1988), silver was detected in 2,195 of over 10,000 surface water samples; the mean and median concentrations in these samples were 1.9 μg/L and 2.0 μg/L, respectively (Eckel and Jacob 1988).

Hem (1970) reported a median silver concentration of 0.23 μg/L in U.S. drinking water. Letkiewicz et al. (1984) analyzed the results of three surveys of U.S. groundwater and surface water used as drinking water supplies. These surveys were the 1969 U.S. Public Health Service Community Water Supply Survey (CWSS 1969), the 1978 EPA Community Water Supply Survey (CWSS 1978), and the 1978 through 1980 EPA Rural Water Survey (RWS). In CWSS 1969, silver was detected (minimum positive value was 0.1 μg/L) in 309 of 677 groundwater supplies, (mean 1.7 μg/L, median 1.3 μg/L, and range 0.1 to 9 μg/L). Silver was detected in 59 of 109 surface water supplies with a mean and median of 1.3 μg/L and a range of 0.1 to 4 μg/L. In CWSS 1978, silver was detected (minimum positive value was 30 μg/L) in 8 of 81 groundwater supplies (range 30-40 μg/L, mean 31.9 μg/L, and median 30 μg/L). Silver was found in 4 of 25 surface water supplies (range 30-40 μg/L, mean 36.2 μg/L, and median 37.5 μg/L). In the RWS conducted between 1978 and 1980, silver was detected (minimum quantifiable concentration apparently was 20 μg/L) in 10 of 71 groundwater supplies (mean and median 40 μg/L and range 20-80 μg/L). Silver was detected in 8 of 21 surface water supplies. The range, mean, and median of these 8 supplies were 20-60 , μg/L, 36.2 μg/L, and 35 μg/L, respectively. Letkiewicz et al. (1984) also summarized information from EPA's Federal Reporting Data System as of 1984, which indicated that 14 public water supplies (13 from groundwater) in the United States reported silver levels above 50 μg/L. Letkiewicz et al. (1984) stated that it is not possible to determine which of these surveys is representative of current levels of silver in the U.S. water supply. The large range in apparent detection limits further limits the usefulness of these data in estimating silver levels in U.S. water supplies.

Silver has been detected with a geometric mean concentration of 6.0 μg/L in groundwater samples from 613 of the 2,783 (22%) hazardous waste sites included in EPA's Contract Laboratory Program (CLP) statistical database (CLP 1988). It has also been detected in surface water samples from 552 of the 2,783 (20%) sites in the CLP statistical database with a geometric mean concentration of 9.0 μg/L (CLP 1988).

5.4.3 Soil

From a series of measurements in Canada, Boyle (1968) estimated that the average silver content of soils (except for mineralized zones such as mining areas) was 0.30 ppm and the average abundance in the earth's crust was 0.10 ppm . The major source of elevated silver levels in cultivated soils is from the application of sewage sludge and sludge effluents (Smith and Carson 1977). The average silver concentration in soils near a lead smelting complex in Kellogg, Idaho (in the Coeur d'hlene River Basin) was 20 ppm (range: 3.2-31 ppm) (Ragaini et al. 1977). Klein (1972) measured soil metal concentrations in the Grand Rapids, Michigan area in order to examine possible relationships between concentrations and land use. Silver concentrations in soils that were classified by land use were 0.13 ppm (residential), 0.19 ppm (agricultural), and 0.37 ppm (industrial) (Klein 1972).

5. POTENTIAL FOR HUMAN EXPOSURE

The Contract Laboratory Program (CLP) statistical database indicates that silver has been detected with a geometric mean concentration of 4.5 ppm in soil samples from 1,807 of 2,783 (65%) hazardous waste sites that have had samples analyzed by the CLP (CLP 1988).

5.4.4 Other Media

Coal has been reported to contain silver at concentrations of up to 10 ppm (Boyle 1968). Klusek et al. (1983) measured the following silver concentrations at a bituminous coal-fired electric generating station: coal -- 0.29 mg/kg; fly ash -- 1.6 mg/kg; and bottom ash -- <0.l mg/kg. In the combustible portions of municipal solid waste, mean silver concentrations were 3 ppm (range: <3-7 ppm) (Law and Gordon 1979). A municipal incinerator was .found to emit particles containing 390 ppm silver (Law and Gordon 1979). The mean and maximum silver concentrations i.n U.S sewage sludge were 225 mg/kg and 960 mg/kg (dry weight), respectively (Bunch 1982). Sludge silver concentrations (mg/kg dry weight) were reported as follows: from sewage treatment plants with industrial or municipal wastes -- 15-120 mg/kg; from plants with photoprocessing effluents as a source -- 450-27,000 mg/kg (Lytle 1984) .

Scow et al. (1981) reported that the median silver concentrations in sewage treatment plant influent and effluent were 0.008 mg/L and 0.002 mg/L, respectively. Treated effluents from a large photographic processing plant contained an average of 0.07 mg/L silver (range: <0.02-0.30 mg/L) in the form of silver thiosulfntc: complexes, silver bromide, and silver sulfide (Bard et al. 1976).

Cunningham and Stroube (1987) collected samples of various foods in 20 U.S. cities between 1979 and 1980. Silver concentrations (mg/kg wet weight) in composite samples of the following food groups were: dairy products -- <0.061; meat, fish, and poultry -- mean 0.015, range 0-87; cereal and grain products -- mean 0.008, range o-0.140; leafy vegetables .-- mean 0.007, range 0-0.039; fruits -- <0.050; oils and fats -- <0.030. The average silver concentration of a mixture of 201. foods prepared to represent the typical U.S. diet was 0.0091 mg/kg dry weight (Iyengar et al. 1987). The average concentration in cow's milk in the United States has been reported to be 0.047 ppm (range:0.037-0.059 ppm) (Murthy and Rhea 1968), EPA (1980a) summarized data on silver content in food as follows: beef -- 0.004-0.024 mg/kg; pork -- 0.007-0.012 mg/kg; mutton and lamb -- 0.006-0.011 mg/kg; tea -- 0.20-2.00 mg/kg (dry weight); mollusks -- 0.1-10.0 mg/kg.

Mean silver concentrations in one brand of nonfilter and filter cigarettes were reported to be 0.18 mg/kg and 0.27 mg/kg, respectively (Nadkarni et al. 1970).

In a summary of 1975-1979 data on fish tissue from EPA's STORET database, the mean concentration of silver in 221 samples was 0.225 mg/kg (wet weight

total fish), with a range of 0.004-1.900 mg/kg (Scow et al. 1981). In Lake Pontchartrain, Louisiana (which is likely to receive substantial inputs of metals from municipal and agricultural activities) silver concentrations in clams and American oyster tissues were 0.4-2.4 mg/kg and 5.5 mg/kg (all dry weight), respectively (Byrne and DeLeon 1986)

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Food and water are the most likely major sources of exposure to natural and anthropogenic silver for the general U.S. population (Letkiewicz et al. 1984). The general population is also exposed through the inhalation of airborne silver and the dental and medical uses of silver. Letkiewicz et al. (1984) estimated that about 50% of the 214 million people in the United States who use public drinking water supplies had silver present in their water at 0.01-10 μg/L; 10-30% may receive water with levels greater than 30 μg/L. They estimated that 46,000 people in the U.S. receive drinking water with silver concentrations exceeding the current U.S. Safe Drinking Water Act maximum contaminant limit of 50 μg/L. Swimming pool water purified with silver-containing systems is another possible source of exposure to silver.

The averaged daily dietary intake (including fluids) of silver has been estimated to be 70 μg/day (Snyder et al. 1975) and 88 μg/day (Kehoe et al. 1940). The average daily dietary intake of two subjects over 30 days was determined to be 35-44 μg/day (Tipton et al. 1966). The silver content of food was estimated at 4.5 μg/day based on the content of a mixture of 201 foods prepared to represent the typical U.S. diet (Iyengar et al. 1987). Most of the U.S. population breathes air containing a maximum of 1.0 ng/m^3 silver, which contributes a maximum of 0.023 μg/day. Drinking water supplies containing 10 μg/L would provide an estimated 20 μg/day of the 70-88 μg/day estimated daily intake. At levels of 30-50 μg/L, drinking water contributes 60-100 μg/day (based on an estimated daily water intake of 2 L) and constitutes the major source of silver intake (Letkiewicz et al. 1984). Although silver has been detected in cigarettes, the average daily intake from smoking has not been determined. A very limited use of silver salts is in purification systems in isolated locations (such as mountain cabins and in space missions) (Silver Institute 1975).

The 1972-1974 National Occupational Hazard Survey (NOHS), conducted by NIOSH estimated that 19,343 workers in 2,163 plants were potentially exposed to silver in 1970 (NIOSH 1976). The largest number of exposed workers were in special trade contracting, primary metal industries, and industries using electrical machinery and electrical equipment and supplies. The occupational groups with the largest number of exposed workers were air conditioning, heating and refrigeration mechanics and repairmen; plumbers and pipefitters; miscellaneous assemblers; welders and flamecutters; and miscellaneous machine operators.

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Preliminary data from a second workplace survey, the 1980-1983 National Occupational Exposure Survey (NOES) conducted by NIOSH, indicated that 67,054 workers, including 15,763 women, in 3,123 plants were potentially exposed to silver in the workplace in 1980 (NIOSH 1984a). These estimates were derived from observations of the actual use of silver (67% of total estimate) and the use of trade name products known to contain the compound (33%). The largest number of workers were exposed in the primary metal industries, business services, health services, instruments and related products industries, and fabricated metal products industries.

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace.

Additional industrial processes which act as potential sources of occupational exposure to silver include the processing of silver chemicals such as silver nitrate and silver oxide for uses such as photography, and smelting and refining of silver-containing ores (DiVincenzo et al. 1985).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The most likely sources of higher than background levels of silver for the general population are ingestion of contaminated food and drinking water, The estimated 46,000 persons in the United States whose drinking water contains more than 50 μg/L silver (attributable to natural and/or anthropogenic sources) would have an estimated daily intake of at least 100 μg/day from water alone (Letkiewicz et al. 1984). Higher levels of silver have been detected in shellfish near industrial or sewage inputs (Byrne and DeLeon 1986; Pesch et al. 1977; Thomson et al. 1984) and are likely to occur in crops grown on sludge-amended soils, in the vicinity of smelters or mining operations, or in areas with naturally high background silver levels.

Elevated atmospheric silver concentrations have been attributed to smelting and refining of silver and other metals, and the use of silver iodide in cloud seeding (Scow et al. 1981). Populations living close to mines may have higher exposures. Approximately 71% of domestic mine production occurs in Idaho, Arizona, and Colorado; the Coeur d'Alene River Basin in Idaho supplies the greatest amount of silver (Drake 1980). Crops grown on soils with elevated silver concentrations (either from anthropogenic sources or from naturally high background levels) or exposed to high ambient atmospheric concentrations are likely to become enriched with silver (Ragaini et al. 1977; Ward et al, 1979).

Silver has been used in lozenges and chewing gums designed to aid the cessation of smoking. Silver acetate in chewing gum has been classified as an over-the-counter smoking deterrent by the Food and Drug Administration (Malcolm et al. 1986). Several cases of high body levels of silver have been

reported (Malcolm et al. 1986). A skin silver concentration thousands of times higher than would be expected as a normal value was found in a patient after an estimated 6 month exposure to silver acetate lozenges (East et al. 1980; MacIntyre et al. 1978).

Scow et al. (1981) estimated that a person developing six rolls of film could be exposed to up to 16 grams of silver through dermal contact with photographic solutions. However, many people use implements or wear gloves during film developing and therefore this is not expected to result in widespread, high level exposures. Inhalation was not expected to be a significant route of uptake during film processing because of the low volatility of silver in solution.

5.7 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silver is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program-of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silver.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. No data exist on the partition coefficients and Henry's law constant for silver and its compounds. A vapor pressure has been determined for silver at very high temperatures (greater than 900°C), but not for any of its compounds. Generally, the fate of silver in the environment is fairly well understood; however, a determination of these environmentally relevant values for silver compounds might provide a more complete estimation of the fate of silver in the environment. Tables 3-7 to 3-12 contain information on the known physical and chemical properties of silver and several important silver compounds.

Production, Use, Release, and Disposal. The production, use, release, and disposal of silver is well characterized and indicates that risk of exposure for the general population is potentially high. Silver and silver compounds are produced and used for a wide variety of common products and

applications, including photographic materials, jewelry, tooth amalgams, medical supplies, and water purification. The extensive production and use of silver leads to a high risk of release to the environment, particularly to soil and water. Silver has been detected in various food products, with the highest levels detected in fish. Silver is both rare and valuable, and consumption exceeds production. Therefore, manufacturers attempt to conserve the metal by limiting releases and recycling instead of disposing of the metal. Methods exist for recovering silver from several waste media. Improvements in capturing released silver before it reaches the environment would be beneficial for both economic and health reasons.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to EPA. The Toxics Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. The factors governing the environmental fate of silver are not well characterized. While silver and its compounds are transported in the air, water, and soil, and are partitioned between these media, the mechanisms of transport and partitioning are not well-defined. No partition coefficients or constants have been determined for silver or its compounds. Little information was found in the available literature on transformation of silver in water or soil. Some microorganisms present in these media may be able to transform si1ver and silver compounds; however, silver is not expected to be significantly transformed in the environment because it is toxic to microorganisms. Further information on the size and flux of environmental compartments and the transport and transformations of silver and silver compounds in the environment would be useful in defining pathways for potential human exposure.

Bioavailability from Environmental Media. Silver is known to be absorbed from the lungs following inhalation exposure to silver dust or air contaminated with silver compounds, but data on the extent and rate of absorption are limited. Silver is also absorbed following oral or dermal exposure to drinking water, solutions and medical products containing silver compounds. No data were located on bioavailability of silver from soil, plant material, or foods. However, silver is found in all these environmental media and it is likely that some silver might be absorbed from these sources. Further information on the bioavailability of silver from contaminated air, water, soil, plants, and other foods would help in assessing the health risk associated with increased exposures that might occur in populations in the vicinity of hazardous waste sites.

Food Chain Bioaccumulation. The data available indicate that silver can bioconcentrate to a limited extent in algae, mussels, clams, and other aquatic

Food Chain Bioaccumulation. The data available indicate that silver can bioconcentrate to a limited extent in algae, mussels, clams, and other aquatic organisms. However, many of the studies that were performed do not conform to the current state of the art in terms of sample size, duration, and analysis of contaminant levels in aquaria. Reliable data would be useful in determining the possibility of biomagnification and in defining pathways for general population exposure, as well as in estimating exposures from NPL site contamination.

Exposure Levels in Environmental Media. Silver has been detected in all environmental media, but most of the data are not current. Current data from EPA's CLP indicate silver is found at levels above background in ground water, surface water and soil near hazardous waste sites. Elevated levels of silver have been detected in shellfish located near sources of silver pollution. Estimates of average daily human intake from air, drinking water, food, and total diet have been calculated. More current information, that better defines major sources and forms of silver, would increase the accuracy of estimates of daily exposure to silver. This information could be used to develop a more thorough representation of the contribution of silver exposure from contamination at hazardous waste sites. Data that better characterize levels in fish and shellfish would aid in identifying populations with potentially high exposures to silver from these sources.

Exposure Levels in Humans. Silver has been detected in the blood, tissues, urine, and feces of humans. The only biological monitoring studies located consisted of small numbers of worker populations in chemical manufacturing industries. Studies that better characterize important sources of general population exposure and define populations with potentially high exposure, such as those located near hazardous waste sites, would be helpful. More specific information concerning the chemical form of silver present at hazardous waste sites would also be useful. These data would assist in developing a more accurate estimate of the potential for silver exposure from hazardous waste sites contaminated with the metal.

Exposure Registries. No exposure registries for silver were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

No long-term research studies on the environmental fate of silver were identified. However, environmental monitoring being conducted in conjunction with remedial investigation/feasibility studies at NPL sites where silver has

been found should add useful information regarding environmental concentrations, chemical species, fate, and transport of the compounds.

No on-going studies or long-term research concerning occupational or general population exposures to silver were identified.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring silver in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify silver. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect silver in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by a trade association such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The analytical methods used to quantify silver in biological and environmental samples are summarized in two tables. Applicable analytical methods for determining silver in biological fluids and tissues are listed in Table 6-1, and those used'for determining silver in various environmental samples are listed in Table 6-2.

6.1 BIOLOGICAL MATERIALS

Trace levels (10^{-6} to 10^{-9} g/g of sample) of silver can be accurately determined in biological samples by several different analytical techniques, provided that the analyst is well acquainted with the specific problems associated with the chosen method. These methods include high frequency plasma torch-atomic emission spectroscopy (HFP-AES), neutron activation analysis (NAA)., graphite furnace (flameless) atomic absorption spectroscopy (GFAAS), flame atomic absorption spectroscopy (FAAS), and micro-cup atomic absorption spectroscopy (MCAAS).

Atomic absorption spectroscopy equipped with various atomizers is the best and most prevalent analytical method used to analyze trace amounts of silver in biological tissues and fluids. GFAAS offers high detectability (subnanogram/gram of sample) and requires relatively small samples for analysis of biological tissues (DiVincenzo et al. 1985; Segar and Gilio 1973). Background absorption from sample matrix components can be a problem, but correction using a deuterium continuum light source is adequate if cautiously applied (Segar and Gilio 1973). The detection limit of silver in biological tissues was $2x10^{-5}$ μg/g of sample.

TABLE 6-1. Analytical Methods for Determining Silver in Biological Materials

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Biological tissues	Digest sample with HNO_3; evaporate to dryness; add glacial acetic acid and adjust to pH 3; add ammonium pyrrolidine dithiocarbamate and extract with methyl-isobutyl ketone; heat organic phase to dryness; dissolve residue with HNO_3	GFAAS	0.0012 µg/g (ketone extract) 0.00002 µg/g (extract after re-version to aque-ous solu-tion)	No data	Segar and Gilio 1974
Whole blood	Dilute sample with water; agitate in ultrasonic bath and analyze	GFAAS	0.5 µg/100 mL	100-120% recovery	DiVincenzo et al. 1985
	Pipette sample into nickel micro-cup and dry at 150•C	MCAAS	0.27 µg/100 mL	98%-110% recovery	Howlett and Taylor 1978
	Add EDTA solution to sample; dilute sample with triton and ammonium hydrogen phosphate; introduce sample solution into a graphite furnace tube; ash sample at 900•C and atomize at 2,000•C	GFAAS	0.015 µg/100 mL	95%-104.5% recovery	Starkey et al. 1987
	Digest sample with 70% perchloric acid and concentrated HNO_3; evaporate to dryness; add 0.4 M NaI and bismuth solution; heat and analyze	HFP-AES or DCP-AES	0.025 µg/100 mL	90%-110% recovery	Nakashima et al. 1975
	Add EDTA solution to sample; add concentrated HNO_3 and shake vigorously; centrifuge at 5,000 g, separate supernatant and analyze	GFAAS	0.24 µg/ 100 mL	98% recovery	Vince and Williams 1987
Hair	Wash sample with benzene; filter solution on paper disk and dry disk; insert sample into quartz tube open from both ends; wash sample with water at 50•C and irradiate	NAA	0.69 ppm	No data	Dutkiewicz et al. 1978

TABLE 6-1 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Hair (Cont.)	Wash hair with water and air-dry; digest sample with concentrated HNO_3 by heating; cool sample and dilute to required volume with water	GFAAS	0.02 µg/g	90%-95% recovery	DiVincenzo et al. 1985
Feces	Homogenize sample with water and lyophilize; dissolve ash residue with concentrated H_2SO_4 and HNO_3 and evaporate excess acid to dryness; add HNO_3 and dilute to required volume with water	GFAAS FAAS	0.2 µg/g 3.0 µg/g	80%-100% recovery	DiVincenzo et al. 1985
Liver	Dry sample at 100°C overnight; digest with a mixture of 16 M HNO_3 and 12 M HCl at 100°C; centrifuge and decant supernatant; extract remaining lipid with hot water; cool and recentrifuge; evaporate supernatant to a small volume and dilute with water	FAAS	0.34 µg/g	99%-101% recovery	Johnson 1976
	Ash sample overnight at 450°C with HNO_3; dissolve ash with 50% aqueous HCl; filter sample and analyze at 328.1 nm	AAS	0.0001-0.0005 µg/g	88-92% recovery	Pickston et al. 1983
Pulmonary tissues	Fix tissue sample in 10% buffered formalin for 24 hours; dehydrate in alcohol and embed in paraffin; section sample at 7 microns; stain in hematoxylin and eosin solutions	XES and SEM	Seven-micron-thick sections	No data	Brody et al. 1978
Urine	Evaporate sample to dryness; wet ash residue by heating with concentrated H_2SO_4 and HNO_3 and evaporate excess acid to dryness; add HNO_3 and dilute to required volume with water	GFAAS	0.005 µg/L	110%-130% recovery	DiVincenzo et al. 1985
	Adjust sample to pH 2 with HNO_3 and analyze	GFAAS	1.4 µg/L	99%	Vince and Williams 1987

GFAAS = graphite furnace (flameless) atomic absorption spectroscopy; MCAAS = micro-cup atomic absorption spectroscopy; DCP-AES = direct current plasma-atomic emission spectroscopy; HFP-AES = high frequency plasma-torch-atomic emission spectroscopy; NAA = neutron activation analysis; FAAS = flame atomic absorption spectroscopy; AAS = atomic absorption spectrophotometer; XES = X-ray energy spectrometry; and SEM = scanning electron microscopy.

TABLE 6-2. Analytical Methods for Determining Silver in Environmental Samples

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
Simulated solid-waste leaches	Digest sample with a mixture of HNO_3 and HF at 100•C overnight; cool solution and add $HClO_4$; heat until sample is evaporated to dryness; dissolve residue in HCl and water	FAAS	0.568 µg/mL (level 1) 0.473 µg/mL (level 2)	No data	Rains et al. 1984
		DCP-AES	0.53 µg/mL (level 1) 0.38 µg/mL (level 3)	No data	
Rain and stream water	Extract sample with organic solvent; concentrate and analyze atom	GFAAS	ng/mL range	No data	Rattonetti 1974
Fresh water	Add 2% citric acid solution to sample and evaporate solution; add buffer (pH 7.2) and react with succinate dehydrogenase -- chromogenic complex solution	Paper chromatography or micro TLC	1 µg/sample	No data	Devi and Kumar 1981
Commercial condensed milk	Digest sample with 70% perchloric acid and concentrated HNO_3 solution, evaporate solution to almost dryness; dissolve residue in water and add 0.4 M NaI and bismuth solution; heat and analyze	HFP-AES or DCP-AES		89%-94% recovery	Nakashima et al. 1975
Air	Collect sample through a Delbag Mikrosorban filter or General Electric filter; store sample in sealed polyethylene bag; irradiate sample and analyze	NAA	0.13 µg/10 cm^2 (Delbag Mikrosorban filter); 0.008 µg/10 cm^2 (General Electric filter)	No data	Bogen 1973
	Calibrate sampling pump; collect sample at known flow rate; add concentrated HNO_3 and $HClO_4$; heat sample solution to dryness; dissolve residue ash in 4% HNO_3 and 1% $HClO_4$ solution; analyze at 328.3 nm	ICP-AES	26 ng/mL	91%-111% recovery	NIOSH 1984b (method 7300)

TABLE 6-2 (Continued)

Sample Matrix	Sample Preparation	Analytical Method	Sample Detection Limit	Accuracy	Reference
	Collect sample at rate of 20 liter/min using acetyl-cellulose filter and analyze at 328 nm	AAS	$3x10^{-4}$ mg/mL	No data	Soldatenkova and Smirnov 1983
	Filter particulate matter from air; irradiate and count sample	NAA (nondestructive)	0.1 μg/sample	No data	Dams et al. 1970
Raw beef	Prepare ash of sample by heating to 500°C; hydrolyze ash sample with 6 N H_2SO_4 and adjust pH to 1.8-2.0; add 2 N ammonium acetate solution and stir overnight; centrifuge and analyze	GSE	0.013 ppm	No data	Mitteldorf and Landon 1952
Waste water	Digest sample and add 5% potassium citrate, phenolphthalein indicator, and 4 M NaOH until solution turns red; add HNO_3 to decolorize solution; finally add buffer (pH 5), 0.1 M EDTA, 1% sodium lauryl sulfate and 0.5 m/g (3,5-diBr-PADAP) in ethanol; measure absorbance at 570 nm	UV	0.39 ppm	>90% recovery	Hung et al. 1982
Metallic silver	Add 0.3 N HNO_3 to sample and adjust to pH 2.3; extract sample with an automated extraction system	FAAS	0.4 μg/L	No data	Pierce et al. 1975
Eye lotion	Add silver nitrate sample to 95% HNO_3 solution and heat to 80-90°C while agitating; cool and filter solution; react filtrate by shaking with a solution of 0.2% dithizone in chloroform; analyze silver in silver nitrate solution at 400 nm	PD	50 ppm	4% error	Massa 1969

FAAS = flame atomic absorption spectroscopy; DCP-AES = direct current plasma-atomic emission spectroscopy; GFAAS = graphite furnace (flameless) atomic absorption spectroscopy; TLC = thin layer chromatography; HFP-AES = high frequency plasma-atomic emission spectroscopy; NAA = neutron atomic analysis; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; AAS = atomic absorption spectrometry; GSE = graphite spectroscopic electrode; UV = ultraviolet spectrophotometry; PD = photodensitometer; and (3,5-diBr-PADAP) = 2(-3,5-dibromo-2-pyridylazo)-5-diethyl-aminophenol.

Recently, Starkey et al. (1987) modified the GFAAS technique for determining trace levels of silver in the blood of exposed and unexposed individuals. Ethylene diamine tetraacetic acid (anticoagulant) and ammonium hydrogen phosphate buffer (matrix modifier) were added to blood samples prior to analysis. Starkey and co-workers indicated that the GFAAS technique is highly selective and sensitive and does not require a complex sample pretreatment (ashing and digestion with strong acids). A detection limit of $15x10^{-3}$ μg/l00 mL of sample was reported.

Howlett and Taylor (1978) used an atomic absorption spectroscopy fitted with a micro-cup assembly (MCAAS) for determining silver levels in human whole blood. The MCAAS technique affords a rapid, precise, and relatively simple method for the measurement of silver in blood. Furthermore, this technique requires no sample preparation prior to analysis except pipetting and drying. A detection limit level of 0.27 μg/l00 mL of blood sample was measured. Howlett and Taylor (1978) noted that repeated measurement of silver in blood using a single nickel cup showed a gradual decrease in sensitivity.

FAAS technique has been successfully used to detect levels of silver in post-mortem human liver; the detection limit for this method was 0.34 μg/g (Johnson 1976).

HFP-AES can determine ng amounts of silver in a small sample of human blood. Prepared human blood sample was introduced into the atomizer chamber as an aerosol, formed by nebulization of the sample solution (Nakashima et al. 1975). The authors noted that the sensitivity of the HFP-AES technique was improved by eliminating moisture in the aerosol with a second condenser at -3 to -5°C. The use of bismuth as a coprecipitate showed an enhancing effect on the silver emission at 328.06 nm. A detection limit of 0.25 μg/l00 mL of sample was attainable. Advantages of the HFP-AES methodology include freedom from most types of chemical interference, high sensitivity, and multielemental capability. However, this technology might have to be adapted to currently available instrumentation in order to be useful. The presence of spectral interferences is a disadvantage of plasma emission spectroscopy. These interferences are caused when a sample contains elements that have analytical emission lines that overlap the line chosen for the analyte. Blood is particularly troublesome because of high concentration of iron. Iron has a very complex emission spectrum. Also, the analytical line for silver used in the Nakashima et al. paper has interference from manganese. For this reason, the blood is subjected to dangerous perchloric acid/nitric acid digestion and preconcentration of silver ion prior to analysis. Other inherent disadvantages of HFP-AES include the employment of time-consuming procedure, the need for standard additions for accurate quantification, and its high costs when compared to GFAAS. Unless a laboratory is already furnished with the instrumentation, purchase of HFP-AES is not recommended for the analysis of silver alone. GFAAS or even DCP-AES could be employed for the determination of silver in biological samples.

Owing to its high sensitivity, the NAA technique has been widely employed for determination of trace elements (including silver) in biological and environmental samples. The NAA technique is based on interaction of the nuclei of individual silver atoms of the sample with neutron irradiation, resulting in the emission of γ-rays (photons). The radioactivity of the irradiated sample is measured with a high-resolution lithium-drifted germanium detector. The long-lived, metastable ^{110m}Ag isotope of silver was formed following irradiation of human hair samples. A half-life of 250.4 days for ^{110m}Ag gives ample time to initiate counting after an irradiation and cooling period (Dutkiewicz et al. 1978). The authors noted a detection limit for silver of 0.69 ppm in human hair. (See Section 2.5 for a discussion of the disadvantages of using hair samples for monitoring exposure to silver.) A disadvantage of NAA is that it is a very expensive technique and may not be readily available in most laboratories.

DiVincenzo et al. (1985) employed the GFAAS technique to evaluate human samples for biological monitoring of silver exposure levels in the workplace. The authors determined the total silver concentration in urine, blood, feces, and hair with detection limits of 0.005 μg/L,0.5 μg/100 mL, 0.2 μg/g, and 0.02 μg/g, respectively.

Scanning electron microscopy (SEM) in concert with x-ray energy spectrometry (XES) has been used to detect silver in pulmonary, lacrimal sac, and skin tissues of individuals with diffuse interstitial lung disease, chronic dacryocystitis, and skin disorders, respectively (Brody et al. 1978; Loeffler and Lee 1987; Tanita et al. 1985). Brody et al. (1978) observed particles of preselected lesions of human pulmonary tissue magnified to 300x by SEM, and the silver content was analyzed by XES. The authors noted that SEM and XES techniques permit a rapid and conclusive determination of silver, silver compounds, and complexes in tissue lesions.

6.2 ENVIRONMENTAL SAMPLES

Atomic absorption and plasma emission spectroscopy are perhaps the most widely used analytical techniques for the determination of silver levels in air, soil, and water. Rains et al. (1984) employed atomic absorption spectroscopy with flame atomization (FAAS) and direct current plasma-atomic emission spectroscopy (DCP-AES) to determine silver levels in solid-waste leachate. In the FAAS technique, a diluted solution of the sample following ashing and digestion is sprayed into a flame by means of a nebulizer. The high temperature causes formation of atoms, which can be observed (at 328.1 nm resonance line) by absorption spectroscopy. The authors noted that interference encountered by the FAAS technique was largely alleviated by the use of 1% solution of ammonium dibasic phosphate buffer as a matrix modifier. In the DCP-AES technique, Rains and co-workers observed silver as a broad band emission at 328.068 nm resonance line. Addition of lithium carbonate to sample solution

reduces the inter-element interferences observed in unbuffered direct-current plasmas, but does not significantly degrade DCP-AES detection limits. Detection limits of silver in solid-waste leachate sample by FAAS and DCP-AES techniques were 0.473×10^{-6} g/mL sample and 0.38×10^{-6} g/L sample, respectively (Rains et al. 1984).

GFAAS technique is more sensitive than FAAS methodology for determination of silver in water samples. Rain and stream water have been analyzed by GFAAS technique to detect silver at ng/mL levels (Rattonetti 1974).

Inductively coupled argon plasma with atomic emission spectroscopy (ICP-AES) has been recommended by NIOSH (method 7300) for determining silver in air. ICP-AES offers multi-element capabilities and high sensitivity but spectral (background) interference can be a problem (NIOSH 1984b). The EPAestablished analytical test procedure (method 200.7) to analyze dissolved, suspended or total silver in drinking water, surface water, and domestic and industrial wastewaters employs the ICP-AES technique (EPA 1987a). An estimated detection limit of 7.0×10^{-6} g silver/L sample was measured.

Neutron activation analysis (NAA) methodology has been used to determine silver levels in environmental samples. Bogen (1973) reported a detection limit of 8×10^{-9} g silver/l0 cm^2 filter. The author indicated that the use of high-resolution lithium-drifted-germanium detection allows multi-elemental analysis to be performed in a single measurement without any chemical pretreatment of the air sample. A highly precise, sensitive, and nondestructive computer-assisted NAA technique for the determination in air of multi-element particulate matter has been designed by Dams et al. (1970). The authors reported a detection limit of 1×10^{-7} g silver/sample. The NAA technique by Bogen (1973) and Dams et al. (1970), utilizes the long-lived isotope of silver (^{110m}Ag) for quantifying silver levels in air. The faster nondestructive NAA technique developed by Dams et al. (1970) utilizes the short-lived isotope ^{110}Ag (half-life = 24.6 seconds) to detect silver in air following an 18-second neutron irradiation of air sample. Hence, counting can be initiated after an irradiation and cooling period of a few minutes.

Hung et al. (1982) developed a sensitive and selective method for silver analysis by reacting silver (I) with 2(-3,5-dibromo-2-pyridylazo)-5-diethyl amino phenol in the presence of an anionic surfactant, sodium lauryl sulfate. The ternary complex formed is red and exhibits an absorption peak at 570 nm. Hung and his co-workers employed EDTA as a chelating agent, thereby reducing the interference of common ions. Recoveries were good, and a detection limit of 0.39 ppm of silver was achieved.

Paper chromatographic, micro thin-layer chromatographic (TLC) and photodensitometric (PD) methods have also been successfully used to determine levels of silver compounds in freshwater and eye lotion samples (Devi and Kumar 1981; Massa 1969). Simple paper and micro thin layer chromatographic (TLC) techniques were employed by Devi and Kumar (1981) to detect and quantify

trace (40 ppm) levels of silver nitrate in fresh water. Devi and Kumar reacted a prepared silver nitrate sample with succinate dehydrogenase enzymechromogenic reagent complex solution prior to paper chromatographic or micro TLC analysis. The metals are recognized by their ability to inhibit the enzymatic formation of a pink reaction product.

Soil samples have been analyzed for silver by AAS (Klein 1972), NAA, and x-ray fluorescence analysis (Ragaini et al. 1977). No statements on the sensitivity, accuracy, or precision of these methods for soil analysis were presented in the brief description of these methods.

6.3 ADEQUACY OF THE DATABASE

Section 104 (i) (5) of CERCLA, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of silver is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of silver.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Existing methods of measuring levels of silver in blood, urine, feces, hair, and tissues are extremely sensitive and can measure levels in the low ppm to ppt. These methods are accurate and reliable and can be used to measure both background levels of exposure and levels at which biological effects occur. No additional analytical methods for determining trace levels of silver in biological materials are needed.

Highly sensitive methods exist to measure silver concentrations in blood, urine, hair, and skin samples of individuals showing the few health effects that have been associated with silver exposure. These methods are also able to accurately measure background levels in the population. No additional analytical methods appear to be needed for the known biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Sophisticated and highly refined methods are available

to detect trace levels of silver and its compounds in air, solid waste leachate, water (the medium of most concern for human exposure), food, and other environmental media. These methods can accurately measure background levels in environmental samples, as well as levels at which health effects occur. There are no known deficiencies in the analytical methods for determining silver in environmental media, and no additional analytical methods appear to be necessary.

6.3.2 On-Going Studies

No on-going studies concerning techniques for measuring and determining silver in biological and environmental samples were located.

7. REGULATIONS AND ADVISORIES

Silver is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987b).

No international regulations pertaining to silver were found. The national and state regulations and guidelines regarding silver in air, water, and other media are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Silver

Agency	Description	Value	Reference
	National		
Regulations:			
a. Air:			
OSHA	PEL TWA (metal and soluble compound)	0.01 mg/m^3	OSHA 1988b (29 CFR 1910.1000)
b. Water:			
EPA ODW	Drinking water MCL[a]	0.05 mg/L	EPA 1987d (40 CFR 141)
	Proposed drinking water SMCL	0.09 mg/L	EPA 1989b
	Permissible levels in bottled water	0.05 mg/L	FDA 1988a (21
FDA			CFR 103.35)
c. Other:			
EPA OSW	Silver nitrate designated as hazardous waste substance	No data	EPA 1987a (40 CFR 116.4)
EPA OERR	Reportable Quantity (RQ)		EPA 1988b (40
	(silver and compounds)	1000 lb	CFR 302.4)
	(silver nitrate)	1 lb	
EPA OTS	Toxic chemical release reporting; community right-to-known (proposed) (silver and compounds)	No data	EPA 1987b (52 FR 21152)
OSHA	Meets proposed medical records rule	No data	OSHA 1988a (29 CFR 1910.20)
Guidelines:			
a. Air:			
ACGIH	TLV TWA:		
	Silver metal dust	0.1 mg/m^3	ACGIH 1986
	Airborne soluble silver compounds	0.01 mg/m^3	
NIOSH	Recommended exposure limit	0.01 mg/m^3	NIOSH 1985
NIOSH	IDLH (silver and soluble silver compounds)	0.01 mg/m^3	NIOSH 1985
b. Water:			
EPA ODW	Recommended drinking water limits	0.05 mg/L	EPA 1985a
EPA OWRS	Ambient water quality criteria to protect human health ingesting water and organisms	0.05 mg/L	EPA 1980b (45 FR 79318)
c. Other:			
EPA	RfD (oral)	3x10^{-3} mg/kg/day	IRIS 1989
EPA ODW	Carcinogen classification	Group D[b]	EPA 1988a
	State		
	Regulations:		
a. Water:	Maximum concentration levels in drinking water:	0.05 mg/L	CELDS 1988
Alabama			
Alaska			
Arkansas			
Arizona			
California			
Colorado			
Connecticut			
Delaware			
District of Columbia			
Florida			
Hawaii			

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
Idaho			
Illinois			
Indiana			
Kansas			
Kentucky			
Louisiana			
Maine			
Maryland			
Massachusetts			
Michigan			
Mississippi			
Minnesota			
Missouri			
Montana			
Nebraska			
Nevada			
New Hampshire			
New Mexico			
New York			
North Carolina			
North Dakota			
Ohio			
Oklahoma			
Oregon			
Pennsylvania			
Rhode Island			
South Carolina			
South Dakota			
Tennessee			
Texas			
Utah			
Vermont			
Virginia			
Washington			
West Virginia			
Wisconsin			
Wyoming			
	Groundwater concentration limits[c]:	0.05 mg/L	CELDS 1988
Colorado			
Indiana			
Kentucky			
Massachusetts			
Nevada			
New Mexico			
New York			
Wisconsin		0.05 mg/L	WDHSS 1989

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Value	Reference
Arizona Mississippi New Jersey New York South Dakota Virginia	Water quality criteria[d]	0.05 mg/L	CELDS 1988

[a]The EPA has proposed to delete the MCL for silver (EPA 1989b).
[b]Group D. Not classifiable as to carcinogenicity in humans.
[c]The classification of groundwater by future use may vary between states.
[d]The criteria upon which this value is based may vary between states, e.g., recreation aquatic life, etc.

ACGIH = American Conference of Government Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IDLH = Immediately Dangerous to Life or Health; MCL = Maximum Contaminant Level; NIOSH = National Institute for Occupational Safety and Health; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RfD = Reference Dose; RQ = Reportable Quantity; SMCL = Secondary Maximum Contaminant Level; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of specified in the toxicological profiles.

Adsorption Coefficient (Koc) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the condentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) -- The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Developmental Toxicity -- The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

9. GLOSSARY

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo -- Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO}) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO}) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

9. GLOSSARY

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (Kow) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

9. GLOSSARY

Reproductive Toxicity -- The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity -- This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen -- A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX

PEER REVIEW

A peer review panel was assembled for silver. The panel consisted of the following members: Dr. Rajendar Abraham, Abraham Associates Limited, Albany, NY; Dr. Thomas Hinesly, University of Illinois, IL; Dr. Arthur Furst, University of San Francisco, CA; Dr. Ernest Foulkes, University of Cincinnati, OH. These experts collectively have knowledge of silver's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104 (i) (13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A joint panel of scientists from ATSDR and EPA has reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the Agency for Toxic Substances and Disease Registry.

EFSA Journal 2016;14(1):4364

SCIENTIFIC OPINION

Scientific opinion on the re-evaluation of silver (E 174) as food additive[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The present opinion deals with the re-evaluation of the safety of silver (E 174) when used as a food additive. Silver in food additive E 174 is present in its elemental form. The Panel noted that there are data gaps and concerns to be addressed to conduct a risk assessment with respect to the use of silver (E 174): lack of data on toxicity studies on elemental silver or the food additive (E 174); unknown particle size distribution of the food additive (E 174); evidence of the release of silver ions from elemental silver, which may be of concern. However, the extent of the release of the silver ions is unknown in the case of silver (E 174). The Panel concluded that the information available was insufficient to assess the safety of silver as food additive. The major issues included chemical identification an d characterisation of silver E 174 (e.g. quantity of nanoparticles and release of ionic silver) and similar information on the material used in the available toxicity studies. Therefore, the Panel concluded that the relevance of the available toxicological studies to the safety evaluation of silver as a food additive E 174 could not be established. The Panel recommended that the specifications for E 174 should include the mean particle size and particle size distribution (± SD), as well as the percentage (in number) of particles in the nanoscale (with at least one dimension below 100 nm), present in the powder form of silver (E 174) used as a food additive. The methodology applied should comply with the EFSA Guidance document, e.g. scanning electron microscopy (SEM) or transmission electron microscopy (TEM). The Panel recommended that additional data in line with the current Guidance document on evaluation of food additives would be required.

KEY WORDS

Silver, E 174, food colour

[1] On request from the European Commission, Question No EFSA-Q-2011-00346, adopted on 10 December 2015.

[2] Panel members: Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Birgit Dusemund, Maria Jose Frutos, Pierre Galtier, David Gott, Ursula Gundert-Remy, Claude Lambré, Jean-Charles Leblanc, Oliver Lindtner, Peter Moldeus, Alicja Mortensen, Pasquale Mosesso, Agneta Oskarsson, Dominique Parent-Massin, Ivan Stankovic, Ine Waalkens-Berendsen, Rudolf Antonius Woutersen, Matthew Wright and Maged Younes. Correspondence: fip@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Standing Working Group on the re-evaluation of food colours: Fernando Aguilar, Riccardo Crebelli, Alessandro Di Domenico, Maria Jose Frutos, Pierre Galtier, David Gott, Claude Lambré, Jean-Charles Leblanc, Agneta Oskarsson, Jeanne Stadler, Paul Tobback, Ine Waalkens-Berendsen and Rudolf Antonius Woutersen, for the preparatory work on this scientific opinion and EFSA staff members, Federica Lodi, Ana Rincon and Alexandra Tard for the support provided to this scientific opinion. The ANS Panel wishes to acknowledge all European competent institutions, Member State bodies and other organisations that provided data for this scientific output.

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SUMMARY

Following a request from the European Commission (EC), the Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to deliver a scientific opinion re-evaluating the safety of silver (E 174) when used as a food additive.

The Panel based its evaluation on previous evaluations and on the additional literature that became available since then and the data available following a public call for data. The Panel noted that not all original studies on which previous evaluations were based were available.

To assist in identifying any emerging issue or any relevant information for the risk assessment, the European Food Safety Authority (EFSA) has outsourced a contract to deliver an updated literature review on toxicological endpoints, dietary exposure and occurrence levels of silver (E 174) which covered the period up to the end of 2014. Further update has been performed by the Panel.

Silver (E 174) is authorised as a food additive in the European Union (EU) in accordance with Annex II to Regulation (EC) No 1333/2008.[4] Silver (E 174) has been previously evaluated by the EU Scientific Committee for Food (SCF) in 1975 (SCF, 1975) and by the Joint FAO/ WHO Expert Committee on Food Additives (JECFA) in 1977 (JECFA, 1977; 1978). Both committees did not establish an acceptable daily intake (ADI) due to inadequate data.

Silver in food additive E 174 is present in its elemental form. Specifications for silver have been defined in the EU in Commission Regulation (EU) No 231/2012. The purity is specified to be not less than 99.5% for silver-coloured powder or tiny sheets. Silver can also occur in crystalline form as a white metal.

During the last call for data, a study on confectionery pearls coated with silver E 174 was performed, finding that a 20% of the mean total silver concentration in the pearls was released as particles after the water treatment of the pearls (Verleysen et al., 2015).

The Panel noted that in Commission Regulation (EU) No 231/2012, no information is included regarding the particle size of silver powder. According to the Panel, the characterisation of the particle size in the powder of E 174 should be included in the specifications. The fully characterisation should include the particles size distribution together with determination and quantification of any nanoparticulate material.

The Panel noted that silver nanoparticles (AgNPs) are released from confectionary pearls (Verleysen et al., 2015) and nanosilver is unstable and releases ions. The Panel was aware of the extensive database on ionic silver or AgNPs, however, the relevance of these data to the evaluation of silver as a food additive (E 174) was not apparent. Therefore, the Panel considered these data could not be directly applied to the evaluation of the food additive.

In this opinion, only data with non-capped nanoparticles are included. However, when corresponding capped nanoparticles have been studied in the same experiments, also those data are included.

Following oral exposure of animals to ionic silver or AgNPs, silver is systemically available. Silver concentrations in the organs were highly correlated to the size of the nanoparticles concentrations being higher in animals exposed to smaller nanoparticles and to the amount of silver ions released from the AgNPs. Bioavailability seems to be in the range of 2–20% depending on many factors including the animal species.

However, the Panel noted that, due to the many variables involved, the conversion rate of metal silver from nanoparticles to silver ions in biological systems is unknown. Moreover, the formation of

[4] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008.

reactive oxygen species (ROS) from the fraction of AgNPs which may be present in the food additive has not been determined. The rate of both processes depends on the size of particles and their relative surface.

Silver distribution has been reported to all organs and tissues in animals. Silver distribution to the brain following oral exposure has been described in several studies, which is in contrast to the conclusions of previous studies with silver nitrate or lactate, that silver would not cross the blood–brain barrier (van Breemen and Clemente, 1955). However, it is also in the recent studies not clear whether silver is present in the brain endothelial cells or in the brain tissue. Silver ions were also detected in the milk of rat dams receiving a daily oral administration of silver chloride, and in the liver and in the brain of the pups. In rodents, silver is primarily excreted via the bile and faeces, but a small amount is also excreted via the urine.

The Panel noted that only one study described the fate of microsized silver particles in animals (Park et al., 2010). In this study, no silver was detected in any of the tissues of mice given an oral administration of microsized silver particles (323 nm), whereas silver was present in tissues of mice receiving a similar administration of nanosized silver particles (21 to 71 nm).

The Panel was aware that there are many data reporting distribution of silver in various human organs following prolonged exposure to very high doses of silver in different forms. The Panel was also aware that there are numerous data reporting adverse effects of silver due to its use in the medical field (Lansdown, 2010; Maillard and Hartemann, 2013) or as a result of occupational exposure (Drake and Hazelwood, 2005). Overall, the Panel noted that in the case of medical and occupational exposure to silver, the doses and/or the route of exposure (inhalation, no inclusion in a food matrix) were usually irrelevant to the exposure resulting from the use of silver as a food additive.

No toxicity studies were reported on elemental silver.

There are no data available to evaluate the *in vivo* genotoxicity of ionic silver. Concerning AgNPs, the available studies provide clear evidence of a genotoxic potential in various *in vitro* test systems. The *in vivo* oral genotoxicity studies performed provide less conclusive evidence, and do not allow a definitive assessment of the possible genotoxic hazard associated with oral exposure to AgNPs. Overall, the Panel concluded that the available data are inadequate to evaluate the genotoxic hazard associated with the use of silver as food additive.

No studies on the carcinogenic potential of either ionic silver compounds or AgNPs have been identified.

In an oral one-generation reproductive toxicity study with silver acetate in drinking water at dose levels of 0, 0.4, 4 or 40 mg silver acetate/kg body weight (bw)/day (0, 0.26, 2.6 or 26 mg ionic silver/kg bw/day) in rats a no-observed-adverse-effect level (NOAEL) for developmental effects (based on an increased number of pups, pup death and decreased weight gain of pups) of 0.4 mg silver acetate/kg bw/day (0.26 mg ionic silver/kg bw/day) was observed (Documentation provided to EFSA No5). The NOAEL for fertility was 4 mg silver acetate/kg bw/day (2.6 mg ionic silver/kg bw/day).

From the maximum level exposure assessment, mean estimates ranged from < 0.01 to 2.6 µg/kg bw/day across all population groups. Estimates based on the high percentile (95th percentile) ranged from 0 to12 µg/kg bw/day across all population groups.

From the refined estimated exposure scenario in the brand-loyal scenario, mean exposure to silver (E 174) from its use as a food additive ranged from < 0.01 µg/kg bw/day for infants to 2.6 µg/kg bw/day in children. The high exposure to silver (E 174) ranged from 0 µg/kg bw/day for infants to 12 µg/kg bw/day in children. In the non-brand-loyal scenario, mean exposure to silver (E 174) ranged from < 0.01 µg/kg bw/day for infants to 1.6 µg/kg bw/day in children. The high exposure ranged from 0 µg/kg bw/day for infants to 3.2 µg/kg bw/day in children.

The exposure from the food additive and the regular diet (ANSES, 2011) could lead to a mean intake for children around 3.5 µg/kg bw/day (non-brand-loyal scenario). On average, exposure from the food additive would represent around 30% of total dietary exposure to silver.

Overall, the Panel noted that there are data gaps and concerns that need to be addressed in order to conduct a risk assessment with respect to the use of silver (E 174) as food additive:

- Data from toxicity studies on elemental silver or the food additive (E 174) are lacking.
- The particle size distribution of the food additive (E 174) is unknown.
- There is evidence of the release of silver ions from elemental silver, which may be of concern. However, the extent of the release of the silver ions, which depends on multiple factors such as pH and particle size, is unknown in the case of silver (E 174) used as food additive.

The Panel concluded that the information available was insufficient to assess the safety of silver as food additive. The major issues included chemical identification and characterisation of silver E 174 (e.g. quantity of nanoparticles and release of ionic silver) and similar information on the material used in the available toxicity studies. Therefore, the Panel concluded that the relevance of the available toxicological studies to the safety evaluation of silver as a food additive E 174 could not be established.

The Panel recommended that the specifications for E 174 should include the mean particle size and particle size distribution (± SD), as well as the percentage (in number) of particles in the nanoscale (with at least one dimension below 100 nm), present in the powder form of silver (E 174) used as a food additive. The methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2011), e.g. scanning electron microscopy (SEM) or transmission electron microscopy (TEM).

The Panel recommended that additional data in line with the current Guidance document on evaluation of food additives (EFSA, 2012) would be required.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

Regulation (EC) No 1333/2008[5] of the European Parliament and of the Council on food additives requires that food additives are subject to a safety evaluation by the European Food Safety Authority (EFSA) before they are permitted for use in the European Union. In addition, it is foreseen that food additives must be kept under continuous observation and must be re-evaluated by EFSA.

For this purpose, a programme for the re-evaluation of food additives that were already permitted in the European Union before 20 January 2009 has been set up under the Regulation (EU) No 257/2010.[6] This Regulation also foresees that food additives are re-evaluated whenever necessary in light of changing conditions of use and new scientific information. For efficiency and practical purposes, the re-evaluation should, as far as possible, be conducted by group of food additives according to the main functional class to which they belong.

The order of priorities for the re-evaluation of the currently approved food additives should be set on the basis of the following criteria: the time since the last evaluation of a food additive by the Scientific Committee on Food (SCF) or by EFSA, the availability of new scientific evidence, the extent of use of a food additive in food and the human exposure to the food additive taking also into account the outcome of the Report from the Commission on Dietary Food Additive Intake in the EU[7] of 2001. The report 'Food additives in Europe 2000[8]' submitted by the Nordic Council of Ministers to the Commission, provides additional information for the prioritisation of additives for re-evaluation. As colours were among the first additives to be evaluated, these food additives should be re-evaluated with a highest priority.

In 2003, the Commission already requested EFSA to start a systematic re-evaluation of authorised food additives. However, as a result of adoption of Regulation (EU) 257/2010 the 2003 Terms of References are replaced by those below.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Commission asks the European Food Safety Authority to re-evaluate the safety of food additives already permitted in the Union before 2009 and to issue scientific opinions on these additives, taking especially into account the priorities, procedures and deadlines that are enshrined in the Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with the Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives.

[5] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives, OJ L 354, 31.12.2008, p. 16–33.

[6] Commission Regulation (EU) No 257/2010 of 25 March 2010 setting up a programme for the re-evaluation of approved food additives in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives. OJ L 80, 26.3.2010, p. 19–27.

[7] Report from the Commission on Dietary Food Additive Intake in the European Union, Brussels, 01.10.2001, COM (2001) 542 final.

[8] Food Additives in Europe 2000, Status of safety assessments of food additives presently permitted in the EU, Nordic Council of Ministers, TemaNord 2002:560.

ASSESSMENT

1. Introduction

The present opinion deals with the re-evaluation of the safety of silver (E 174) when used as a food additive. Silver (E 174) is authorised as a food additive in the EU in accordance with Annex II to Regulation (EC) No 1333/2008.[9]

Silver (E 174) has been previously evaluated by the EU Scientific Committee for Food (SCF) in 1975 (SCF, 1975), and by the Joint FAO/ WHO Expert Committee on Food Additives (JECFA) in 1977 (JECFA, 1977; 1978). Both committees did not establish an acceptable daily intake (ADI) due to inadequate data. EFSA has also evaluated a number of silver complexes intended for use in food contact materials latest in 2011 (EFSA, 2011) and classified silver in the SCF list 3 with a group of specific migration limit of 0.05 mg/kg food.

The Panel on Food Additives and Nutrient Sources added to Food (ANS) was not provided with a newly submitted dossier and based its evaluation on previous evaluations, additional literature that became available since then and the data available following public calls for data.[10,11,12,13] The Panel noted that not all of the original studies on which previous evaluations were based were available for this re-evaluation.

To assist in identifying any emerging issue or any relevant information for the risk assessment, EFSA has outsourced a contract to deliver an updated literature review on toxicological endpoints, dietary exposure and occurrence levels of silver (E 174), which covered the period up to the end of 2014. The Panel has performed further update.

2. Technical data

2.1. Identity of the substance

Silver in food additive E 174 is present in its elemental form. The chemical element has atomic number 47 and symbol Ag: it has an atomic weight of 107.87 g/mol, Chemical Abstract Service (CAS) Registry No 7440-22-4, and EC No (or European Inventory of Existing Commercial chemical Substances (EINECS) number) 231-131-3. According to Commission Regulation (EU) No 231/2012,[14] silver occurs as silver-coloured powder or tiny sheets.

Silver is also described to occur in a crystalline form as a white, lustrous, soft and ductile/malleable metal (Cotton et al., 1999; Holler et al., 2007; Kirk-Othmer, 2006). It has a density of 10.5 g/cm^3 at 20°C and a melting point of 962°C. Pure silver has the highest thermal and electrical conductivities of all metals.

[9] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives. OJ L 354, 31.12.2008.

[10] Call for scientific data on food colours to support re-evaluation of all food colours authorised under the EU legislation. Published: 8 December 2006. Available from: http://www.efsa.europa.eu/en/dataclosed/call/afc061208.htm

[11] Call for scientific data on Silver (E 174) and Gold (E 175), used as food colours. Published: 23 February 2011. Available from: http://www.efsa.europa.eu/en/dataclosed/call/ans110224

[12] Call for food additives usages level and/or concentration data in food and beverages intended for human consumption. Available from: http://www.efsa.europa.eu/en/dataclosed/call/datex140310.htm

[13] Call for scientific data on selected food additives permitted in the EU- Extended deadline: 1 September 2014 (batch A), 1 November 2014 (batch B).http://www.efsa.europa.eu/en/dataclosed/call/140324.htm

[14] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. OJ L 83 of 22.3.2012, p. 1–295.

2.2. Specifications

Commission Regulation (EU) No 231/2012 on specifications for food additives lays down the specifications for silver (E 174) used as a food additive (Table 1). JECFA has not defined specifications for silver.

Table 1: Specifications established for silver (E 174) according to Commission Regulation (EU) No 231/2012.

	Commission Regulation (EU) 231/2012
Synonyms	Argentum
Definition	
Colour Index No	77820
EINECS No	231-131-3
Chemical name	Silver
Chemical formula	Ag
Atomic weight	107.87
Assay	Content not less than 99.5% Ag
Description	Silver-coloured powder or tiny sheets
Identification	—
Purity	—

The Panel noted that, according to the limited information provided by industry, silver used as food colour may have a minimum certified silver content of 99.999% (total impurities, ≤ 10 mg/kg) (see Section 2.3). During the last call for data, a study on confectionery pearls coated with silver E 174 was performed, finding that a 20% of the mean total silver concentration in the pearls was released as particles after the water treatment of the pearls (Verleysen et al., 2015).

In response to a request from EFSA on the silver particles size, an interested party (Documentation provided to EFSA No4) provided information on particle size distribution of the additive gold, in its powdered form and suggested that these data could be also valid for silver. The Panel did not agree with this proposal.

The Panel noted that in Commission Regulation (EU) No 231/2012, no information is included regarding the particle size of silver powder, and therefore the characterisation of the particle size in the powder of E 174 should be included among the specifications. The fully characterisation should include the particles size distribution together with determination and quantification of any nanoparticulate material.

The Panel noted that the manufacturing process of powdered or particulate food additives resulted in material with a range of sizes. Although the mean or median size of the particles is generally significantly greater than 100 nm, a fraction can be present with at least one dimension below 100 nm. The material used for toxicological testing would have contained this nanofraction. The test requirements stipulated in current EFSA guidance documents and EC guidelines for the intended use in the food/feed area apply in principle to unintended nanoforms as well as to engineered nanomaterials (ENM). Therefore, the Panel considers that in principle for a specific food additive containing a fraction of particles with at least one dimension below 100 nm, adequately conducted toxicity tests should be able to detect hazards associated with this food additive including its nanoparticulate fraction. The Panel considers that for the re-evaluation of food additives this procedure would be sufficient for evaluating constituent nanoform fraction in accordance with the recommendation of the EFSA Nano Network in 2014 (EFSA, 2015).

The Panel noted that the coating of AgNPs with different compounds is made with the purpose of improving their stability and dispersability, thus not being relevant for the food additive E 174 where silver is present in its elemental form.

According to product specifications for the commercial products of AgNPs (non-food additive powder), the colours are beige to dark grey or silver < 100nm; grey < 150nm; silver or grey 2–3.5µm; whereas for colloidal suspensions of AgNPs, the colour is pale-yellow (Lok et al., 2007; Liu and Hurt, 2010).

Information on AgNPs has been reported in the Organisation for Economic Co-operation and Development (OECD) report (OECD, 2015). The mean diameters of the AgNPs in the powder were < 55 nm with non-aggregated forms and a size distribution from 6 to 55 nm. The melting point was identified as 961.9°C and a boiling point of 2,212°C. The density at 20°C is ca 10.43–ca 10.49 g/cm3. The tests made with AgNPs coated with different compounds, as citrate or polyvinylpryrolidone (PVP) stabilised AgNPs in colloidal suspensions, demonstrated an excellent stability preventing aggregation of the dispersions. However, these suspensions can be destabilised by changes in the media as low pH and light for the citrate-coated nanoparticles.

Pearlescent pigments surface treatment for confectionery is described in the open patent literature (Myers et al., 2008; Campomanes and Vilches, 2010). They are commercially available under a number of trade name and colours (provide a wide range of colour effects including, but not limited to, silver fine, silver sheen, silver lustre, silver sparkle, gold shimmer, red shimmer, blue shimmer, green shimmer, gold sheen, light gold). A fluid carriers can be used in the surface treatment. The fluid carriers of the invention as described by Myers et al., 2008, 'Pearlescent pigment surface treatment for Confectionery'**,** can include, but are not limited to, a range of different compounds such as acetone, acetylated monoglycerides, different oils or waxes. Because the fluid carrier forms part of the pigmented coating composition which is applied to the surface of a hard candy substrate, it is advantageous to use fluid carriers that contribute little to no moisture to the pigmented coating composition.

2.3. Manufacturing process

Neither the SCF nor JECFA have provided any information concerning the manufacture of silver as food additive. Some data were submitted to EFSA following its public call for data.[15]

Silver is widely distributed in the free state (elemental silver) and in many minerals in which it is found in combination with different elements including sulfur, arsenic, antimony and chlorine: argentite, a sulfide, is the principal ore mineral. These minerals are commonly associated with lead, copper, zinc and gold (Cotton et al., 1999; Kirk-Othmer, 2006). Silver is traditionally extracted by treatment with cyanide solutions in the presence of air; it is also recovered from the work-up of copper and lead ores. The metal obtained is ultimately refined by electro-deposition to a high purity grade: for instance, for the American Society for Testing and Materials International, the minimum standard for commercial silver is 99.90% (ASTM B413). Higher purity grades can be obtained and are readily available from the market. Common impurities are (in descending order) copper, lead, iron and bismuth.

According to the limited information provided by industry as a response to EFSA's call for data (Documentation provided to EFSA, No6), silver used as food colour has a minimum certified silver content of 99.999% (total impurities, ≤ 10 mg/kg). The Panel noted that this certified content is higher than that required by Commission Regulation (EU) No 231/2012. According to the aforementioned reference, production starts from sheets as thin as some tenths of a micron. These sheets are reduced by a mechanical milling process to commercial sizes. Size is controlled by means of different grids

[15] Call for scientific data on Silver (E 174) and Gold (E 175), used as food colours. Published: 23 February 2011. Available from: http://www.efsa.europa.eu/en/dataclosed/call/ans110224

that are mounted on the mill. In case of production of squared leaves, the metal sheets are manually cut by means of a knife. When unsquared leaves are produced, no further cutting operations are performed on the sheets. To eliminate potential microorganisms, silver is heated to not less than 100°C for at least 120 s.

The Panel noted that the response to EFSA's call for data was limited to only one manufacturer of silver, and considered that a manufacturing process concerning a specific case may not be representative of the market situation.

2.4. Methods of analysis in food

A number of methods for analysis of silver in food have been described in the published literature.

One rapid determination method for silver in oysters suing is the so-called 24.6-s neutron activation product ^{110}Ag (Fukushima and Chatt, 2013).

Determination of silver in food (wheat flour or green tea leaf) was described by use of microcolumn high-performance liquid chromatography (Hu et al., 2004).

Flame atomic absorption spectrophotometry has been employed for the determination of silver in foodstuffs (cereals, meat, fish, fats, sugars and preserves, root vegetables, green vegetables, beverages and milk) (Jackson et al., 1980). The level of silver ions released from silver nanocomposites in apple juice has also been measured with atomic absorption spectrometer (Jokar et al., 2014).

The levels of silver in biological samples can also be measured using dispersive liquid-liquid microextraction (DLLME) and graphite furnace atomic absorption spectrometry (GFAAS) (Dittert et al., 2014).

AgNPs detection, characterisation and quantification in pears have been performed by using a combination of techniques as transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy dispersive spectrometer and inductively coupled plasma optical emission spectrometry (ICP-OES) (Zhang et al., 2012). An inductively coupled plasma mass spectrometry (ICP-MS) system with quadrupole mass analyser, multichannel detector was used for the measurement of the silver levels in tomato (Enamorado et al., 2014). The ICP-MS method has been also used for the determination of the levels of silver and other trace elements in muscle tissues of some seafood species as red mullet, grey mullet and tiger prawn (Yarsan et al., 2014).

Detection of AgNPs in aqueous food matrices (e.g. water, coffee or milk) by using particle-induced X-ray emission has also been described (Lozano et al., 2012), as well as by using single particle (SP)-ICP spectrometry for detection in water or migration of silver from nanosilver-polyethylene composite packaging into food simulants (Mitrano et al., 2012; Song et al., 2011). Ramos et al. (2014) have used the asymmetric flow field fractionation coupled with inductively coupled plasma mass spectrometry for the separation, characterisation and quantification of AgNPs in complex nutraceuticals and beverages (Ramos et al., 2014).

A new methodology based on the combination of conventional and advanced TEM methods, ICP-MS and SP-ICP-MS has been applied for the analysis of the AgNPs released from the coating of silver-coloured pearls meant for decoration of pastry (with an average of 8.4 µg Ag/pearl), following a treatment with water. The physico-chemical properties of the particles in the eluted fraction are also characterised by electron diffraction and a combination of high-angle annular dark-field scanning transmission electron microscopy (HAADF-STEM) imaging with energy dispersive X-ray (EDX) spectroscopy and mapping. For the TEM analysis, the silver pearls were treated with water in a proportion of 1 pearl /25 µL water. For the ICP-MS analysis, a proportion of 1 pearl/2 mL water was used for the pearl dissolution and 0.5 mL of this suspension was further diluted in 50 mL of water. A

latter suspension was further diluted 50 and 100 times for analysis (total dilution factors of 5,000 and 10,000, respectively) (Verleysen et al., 2015).

2.5. Reaction and fate in food

The influence of AgNPs on food components has been studied in wheat grains treated with AgNPs stabilised by sodium citrate to prevent them from infections. Significant differences have appeared after the treatment in the gluten due to changes in the protein secondary structure (Nawrocka and Ciesla, 2013).

Beera et al. (2012) reported the presence of silver ions released from AgNPs (69 nm) aqueous suspensions, that contained 39, 59 or 69% silver ions depending on the batch. The silver ion fraction was much lower for colloidal solutions with citrate-coated protein-encapsulated AgNPs (from 2.6 to 5.9% of total Ag and a mean particle size from 15.9 to 19.8 nm) than for non-coated AgNPs aqueous suspensions. The toxicological implications of this *in vitro* study are described in Section 3.2.6.

Following the last call for data, a published study by Verleysen et al. (2015), on the release of AgNPs (< 100 nm) after a water treatment of confectionery pearls consisting of sugar coated with silver (E 174) intended for decoration of pastry was submitted. In this study, the amount of silver reported was of 8.4 µg Ag/g pearl, with a variation of 38% among pearls, and the number of nanoparticles released was quantified representing an amount of 4.4×10^9 Ag nanoparticles/g of pearl. The mass concentration of the detected particles was 1.8 ± 0.6 µg/g pearl. This number represents 20% of the mean total silver concentration in the pearls. The single, aggregated and/or agglomerated particles were characterised in size, shape, crystal structure and chemical composition through different TEM and SP-ICP-MS methods.

The Panel noted that nanosilver is unstable and releases ions through gradual reaction with oxygen and protons or with pre-existing oxide films in fluid media and that the oxidative dissolution is influenced by pH, coatings and ligands (Liu and Hurt, 2010; Liu et al., 2012). Other studies have related the antibacterial activity of AgNPs to their sensitivity of oxidation, being dependent of optimally displayed oxidised surfaces, presented in well-dispersed suspensions. It has also been found that partially oxidised AgNPs have antibacterial activities (Lok et al., 2007).

In contact with air, silver is not very reactive although sulfur and sulfur compounds (e.g. hydrogen sulfide, sulfur dioxide) blacken its surface as Ag_2S is formed (tarnishing) (Kirk-Othmer, 2006).

The Panel noted that with the exception of complex ions, the only stable cationic species is ionic silver (Ag^+); the other oxidation states (Ag^{2+} and Ag^{3+}) are either unstable in water or exist only in insoluble compounds or complexed species. Therefore, the silver ion released from the oxidation of silver should be Ag^+.

2.6. Case of need and proposed uses

Maximum levels of silver (E 174) have been defined in Annex II to Regulation (EC) No 1333/2008 on food additives. These levels are referred by the Panel as maximum permitted levels (MPLs) in this document.

Currently, silver (E 174) is an authorised food additive in the EU at quantum satis (QS) in three food categories (Table 2).

Table 2: MPLs of silver (E 174) in foods according to the Annex II to Regulation (EC) No 1333/2008.

FCS[(a)] Category No	Foods	Restrictions/exceptions	Maximum permitted level (MPL) (mg/l or mg/kg as appropriate)
05.2	Other confectionery including breath-refreshening microsweets	Only external coating of confectionery	Quantum satis
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 4.2.4	Only decoration of chocolates	Quantum satis
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	Only liqueurs	Quantum satis

(a): FCS: Food categorisation System (food nomenclature) presented in the Annex II to Regulation (EC) No 1333/2008.

2.7. Reported use levels of silver (E 174) in food

Most food additives in the EU are authorised at a specific MPL. However, a food additive may be used at a lower level than the MPL. Therefore, information on actual use levels is required for performing a more realistic exposure assessment, especially for those food additives for which no MPL is set and which are authorised according to QS.

In 2011, EFSA launched a public call[16] for scientific data on silver (E 174) used as a food colour, to support the re-evaluation of silver (E 174) authorised under the EU legislation. Among other information, information on the human exposure to the food additive from the different types of food where it is permitted (e.g. consumption pattern and uses, actual use levels and maximum use levels, frequency of consumption and other factors influencing exposure) was requested. In response to this public call, very few usage data on silver (E 174) in the external coating of confectionery and decoration of chocolates were submitted to EFSA by one data provider, FoodDrinkEurope (FDE, formerly CIAA) (Documentation provided to EFSA, No1) (Appendix A).

In addition, in the framework of Regulation (EC) No 1333/2008 on food additives and of Commission Regulation (EU) No 257/2010 setting up a programme for the re-evaluation of approved food additives, EFSA launched a public call[17] for food additives usage level and/or concentration data in food and beverages. Data on silver (E 174) were requested from relevant stakeholders. European food manufacturers, national food authorities, research institutions, academics, food business operators and any other interested stakeholders were invited to submit usage and/or concentration data on silver (E 174) in foods. No information concerning actual use levels of silver (E 174) in food were obtained from the industry in response to this call for data.

According to the GNDP database, silver (E 174) was found to be present in one liqueur (grappa-based liqueur) and few foods (for a total of 34 products between 2010 and now). According to the Mintel GNDP database,[18] in Europe, silver (E 174) is used mostly in sugar confectionery (silver-coated sugar pearls used for decoration purposes and sugar-coated almonds) and less often as external coating of chocolates.

2.8. Information on existing authorisations and evaluations

Silver, used as a food additive, has been previously evaluated by the SCF in 1975 (SCF, 1975). In that evaluation, the SCF did not establish an ADI because of the inadequacy of available biological data, but accepted the continued use for only external colouring and decoration. The full SCF statement

[16] http://www.efsa.europa.eu/sites/default/files/consultation/ans110224.pdf
[17] http://www.efsa.europa.eu/sites/default/files/consultation/140310.pdf
[18] Mintel Global New Products Database (http://www.mintel.com/global-new-products-database). Accessed on 21/9/2015.

reads as follows: 'No specification was available to the Committee. The Committee did not establish an ADI because of the inadequacy of the available biological data but felt able to accept the use of this colour for surface colouring and decoration of food only, without further investigations.' No references were given.

Silver was evaluated by JECFA in 1977 (JECFA, 1977, 1978). The Committee concluded (JECFA, 1978): 'In view of the rare use of this metal and in the absence of knowledge of the exact nature of silver used on or in foods, specifications were not prepared. The data available suggest that this substance might accumulate in certain tissues following long-term exposure. There were, however, insufficient data to evaluate this point fully, nor were any adequate long-term studies available. Thus, no evaluation could be made.'

In 2000, the Scientific Committee on medicinal products and medical devices (SC, 2000) delivered an opinion on the use of silver E 174 in which it is proposed that use of this metal as a colourant be prohibited in medicinal products. This committee stated that 'the potential exposure to silver used as a colouring agent in medicinal products by oral route has to be added to that ingested daily with food and water, and both types of exposure are extremely difficult to quantify. Therefore, it is the Committee's opinion that use of this metal as a colourant be prohibited in medicinal products.'

In 2009, the BfR (Bundesinstitut für Risicobewertung) recommended: 'manufacturers to avoid the use of nanoscale silver or nanoscale silver compounds in foods and everyday products until such time that the data are comprehensive enough to allow a conclusive risk assessment which would ensure that products are safe for consumer health' (BfR Opinion, 2009).

A technical report was submitted to EFSA in 2010 on trace elements in animal nutrition and elements for risk assessment that includes a report on silver (Van Paemel et al., 2010). This report stated that AgNPs were beneficial for growth in weaned piglets, mainly due to their antimicrobial properties. However, excessive ingestion of silver is associated with copper and selenium deficiency in poultry.

In 2011, EFSA published a scientific opinion on the safety evaluation of the substance silver zeolite A (silver zinc sodium ammonium alumino silicate), silver content 2–5% for use in food contact materials (EFSA, 2011a). The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) classified silver zeolite in the SCF list 3 with a specific migration limit of 0.05 mg Ag/kg food based on the human no-observed-adverse-effect level (NOAEL) of about 10 g/kg silver for a total lifetime oral intake (WHO, 2008) for drinking water.

In 2014, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) issued a report on the evaluation of environmental risks linked to the exposure to AgNPs (ANSES, 2015). In this document, the presence of AgNPs in consumer products in different fields including the food sector has been reviewed together with the toxicological studies. This document reported that it was not clear whether the observed effects in some tests *in vitro* and *in vivo* are due exclusively to the silver ions or to the AgNPs or to a combined effect of the ions and nanoparticles.

2.9. Exposure assessment

2.9.1. Food consumption data used for exposure assessment

2.9.1.1 EFSA Comprehensive European Food Consumption Database

Since 2010, the EFSA Comprehensive European Food Consumption Database (Comprehensive Database) has been populated with national data on food consumption at a detailed level. Competent authorities in the European countries provide EFSA with data on the level of food consumption by the individual consumer from the most recent national dietary survey in their country (cf. Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure

Assessment' (EFSA, 2011b). New consumption surveys recently added in the Comprehensive database were also taken into account in this assessment.[19]

The food consumption data gathered by EFSA were collected by different methodologies and thus direct country-to-country comparisons should be interpreted with caution. Depending on the food category and the level of detail used for exposure calculations, uncertainties could be introduced owing to possible underreporting by subjects and/or misreporting of the consumption amounts. Nevertheless, the EFSA Comprehensive Database represents the best available source of food consumption data across Europe at present.

Food consumption data for the following population groups: infants, toddlers, children, adolescents, adults and the elderly were used for the exposure assessment. For the present assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 3).

Table 3: Population groups considered for the exposure estimates of silver (E 174)

Population	Age range	Countries with food consumption surveys covering more than one day
Infants	From 4 months up to and including 11 months of age	Bulgaria, Denmark, Finland, Germany, Italy, UK
Toddlers	From 12 months up to and including 35 months of age	Belgium, Bulgaria, Denmark, Finland, Germany, Italy, Netherlands, Spain, UK
Children [(a)]	From 36 months up to and including 9 years of age	Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Latvia, Netherlands, Spain, Sweden, UK
Adolescents	From 10 years up to and including 17 years of age	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Italy, Latvia, Spain, Sweden, UK
Adults	From 18 years up to and including 64 years of age	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Romania, Spain, Sweden, UK
The elderly [(a)]	From 65 years of age and older	Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Romania, Sweden, UK

(a): The terms children and the elderly correspond, respectively, to other children and the merge of the elderly and the very elderly in the Guidance of EFSA on the 'Use of the EFSA Comprehensive European Food Consumption Database in Exposure Assessment' (EFSA, 2011b).

Consumption records were codified according to the FoodEx classification system (EFSA, 2011c). Nomenclature from the FoodEx classification system has been linked to the Food Classification System (FCS) as presented in Annex II of Regulation (EC) No 1333/2008, part D, to perform exposure estimates. In practice, FoodEx food codes were matched to the FCS food categories.

2.9.1.2 Food categories selected for the exposure assessment of silver (E 174)

The food categories in which the use of silver (E 174) is authorised were selected from the nomenclature of the EFSA Comprehensive Database (FoodEx classification system food codes), at the most detailed level possible (up to FoodEx level 4) (EFSA, 2011c).

No use levels were reported for liqueurs, therefore this food category was not taken into account in the present estimate. This may have resulted in an underestimation of the exposure.

[19] Available online at: http://www.efsa.europa.eu/en/datexfoodcdb/datexfooddb.htm

Silver (E 174) is authorised in the two other food categories: Other confectionery including breath-freshening microsweets (FCS 05.2) and Decorations, coatings and fillings (FCS 05.4) as coating. The Panel noted that silver (E 174) is probably present on few chocolates or confectionary products only. However, such details on the presence or not of silver (E 174) on chocolates and confectionery are not available in the FoodEx nomenclature. In order to provide a more realistic estimate, some food items were removed from the list of confectionery or chocolates as they usually do not contain silver (E 174) (e.g. liquorice candies, jelly candies, gum drops, nougats, halva, chocolate bars, chocolate cream). The other products may contain silver (E 174) and were taken into account in the present estimate. It has been considered by the Panel that such products with silver are not consumed on a daily basis (special occasion e.g. Christmas, Easter, etc.), then, an assumption of consumption of 10 times per year has been applied.

Added to that, silver (E 174) is only used at low level as coating ingredient in the product (below 1%). This percentage was applied to the consumption of cocoa products and confectionery selected, to retrieve consumption of the food additive.

2.9.2. Exposure to silver (E 174) from its use as a food additive

The Panel estimated chronic exposure to silver (E 174) for the following population groups: infants, toddlers, children, adolescents, adults and the elderly. Dietary exposure was calculated by multiplying silver (E 174) concentrations reported in Appendix A for each food category with their respective consumption amount per kilogram of body weight for each individual in the Comprehensive Database. The exposure per food category was subsequently added to derive an individual total exposure per day. These exposure estimates were averaged over the number of survey days, resulting in an individual average exposure per day for the survey period. Surveys with only one day per subject were excluded as they are considered not adequate to assess repeated exposure.

This was carried out for all individuals per survey and per population group, resulting in distributions of individual exposure per survey and population group (Table 3). Based on these distributions, the mean and 95th percentile of exposure were calculated per survey for the total population and per population group. High percentile exposure was only calculated for those population groups where the sample size was sufficiently large to allow calculation of the 95th percentile of exposure (EFSA, 2011b). Therefore, in this assessment, high levels of exposure for infants from Italy and for toddlers from Belgium, Italy and Spain were not included. Thus, for this assessment, food consumption data were available from 33 different dietary surveys carried out in 19 European countries (Table 3).

Exposure assessment of silver (E 174) was carried out by the ANS Panel based on (1) maximum reported use levels (defined as the *maximum level exposure assessment scenario*) and (2) reported use levels (defined as the *refined exposure assessment scenario*) as provided to EFSA by industry. These two scenarios are discussed in detail below.

2.9.2.1 Maximum level exposure assessment scenario

The regulatory maximum level exposure assessment scenario is based on the MPLs as set in Annex II to Regulation (EC) No 1333/2008. As silver (E 174) is authorised according to QS in all food categories, a 'maximum level exposure assessment' scenario was estimated based on the maximum reported use levels provided by industry (Appendix A), as described in the EFSA Conceptual framework (EFSA ANS Panel, 2014).

The Panel considers the exposure estimates derived following this scenario as the most conservative as it is assumed that the consumer will be continuously (over a lifetime) exposed to silver (E 174) present in food at the maximum reported use levels.

2.9.2.2 Refined exposure assessment scenario

The refined exposure assessment scenario is based on use levels reported by industry. This exposure scenario can consider only food categories for which the above data were available to the Panel.

Appendix A summarises the concentration levels of silver (E 174) used in the refined exposure assessment scenario. Based on the available data set, the Panel calculated two refined exposure estimates based on different model populations:

- The brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to silver (E 174) present at the maximum reported use level for one food category. This exposure estimate is calculated as follows:
  - combining food consumption with the maximum reported use level for the main contributing food category at the individual level;
  - using the mean of the typical reported use levels for the remaining food categories.
- The non-brand-loyal consumer scenario: It was assumed that a consumer is exposed long-term to silver (E 174) present at the mean reported use levels in food. This exposure estimate is calculated using the mean of the typical reported use levels for all food categories.

The Panel noted that only two food categories out of the three food categories in which the use of silver (E 174) is authorised could be taken into account. If, nevertheless, silver (E 174) is used in the remaining food category of liqueurs for which concentration data were not available, the calculated exposure estimates might result in underestimation of the actual exposure to silver (E 174).

2.9.2.3 Anticipated exposure to silver (E 174)

Table 4 summarises the estimated exposure to silver (E 174) from its use as a food additive in six population groups (Table 3) according to the different exposure scenarios (Sections 2.9.2.1 and 2.9.2.2). Detailed results per population group and survey are presented in Appendix B.

Table 4: Summary of anticipated exposure to silver (E 174) from its use as a food additive in the maximum level exposure assessment scenario and in the refined exposure scenario, in six population groups (minimum–maximum across the dietary surveys in µg/kg body weight (bw)/day)

	Infants (4-11 months)	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
Mean	< 0.01–0.17	0.07–1.9	0.22–2.6	0.10–2.2	0.03–0.65	0.02–0.18
High level	0.0–0.79	0.32–4.3	1.1–12.0	0.60–8.6	0.20–3.6	0.11–0.70
Refined estimated exposure scenario						
Brand-loyal scenario						
Mean	< 0.01–0.17	0.07–1.7	0.21–2.6	0.09–2.1	0.03–0.64	0.02–0.17
High level	0.0–0.79	0.32–4.1	1.1–12.0	0.60–8.6	0.20–3.5	0.11–0.67
Non-brand-loyal scenario						
Mean	< 0.01–0.17	0.03–1.6	0.18–1.0	0.09–0.77	0.03–0.22	0.02–0.15
High level	0.0–0.69	0.23-2.7	0.87–3.2	0.60–2.3	0.19–0.97	0.09–0.64

2.9.3. Main food categories contributing to exposure to silver (E 174)

Table 5: Main food categories contributing to exposure to silver (E 174) using maximum usage levels (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

FCS category number	FCS Food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys)[a]					
05.2	Other confectionery including breath-freshening microsweets	10.9–37.2 (4)	14.9–56.5 (10)	11.9–86.6 (18)	8.5–91.8 (17)	5.5–80.4 (16)	9.2–76.2 (13)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 04.2.4 – only decorations of chocolates	62.8–100 (6)	43.5–100 (10)	13.4–88.1 (18)	8.2–91.5 (17)	19.6–96.2 (17)	23.8–97.0 (14)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.

Table 6: Main food categories contributing to exposure to silver (E 174) using the brand-loyal refined exposure scenario (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

FCS category number	FCS Food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys)[a]					
05.2	Other confectionery including breath-freshening microsweets	10.9–37.2 (4)	7.2–56.4 (9)	8.4–86.4 (18)	6.5–91.8 (16)	7.3–80.2 (15)	8.2–75.8 (13)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 04.2.4 – only decorations of chocolates	62.8–100 (6)	43.6–100 (10)	13.6–91.6 (18)	8.2–95.1 (17)	19.8–96.2 (17)	24.2–98.1 (14)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.

Table 7: Main food categories contributing to exposure to silver (E 174) using the non-brand-loyal refined exposure scenario (> 5% to the total mean exposure) and number of surveys in which each food category is contributing

FCS category number	FCS Food category	Infants	Toddlers	Children	Adolescents	Adults	The elderly
		Range of % contribution to the total exposure (number of surveys)[a]					
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 04.2.4 – only decorations of chocolates	99.9–100 (6)	99.9–100 (10)	99.3–100 (18)	98.7–100 (17)	99.5–100 (17)	99.6–100 (14)

(a): The total number of surveys may be greater than the total number of countries as listed in Table 3, as some countries submitted more than one survey for a specific population.

2.9.4. Uncertainty analysis

Uncertainties in the exposure assessment of silver (E 174) have been discussed above. In accordance with the guidance provided in the EFSA opinion related to uncertainties in dietary exposure assessment (EFSA, 2006), the following sources of uncertainties have been considered and summarised in Table 8.

Table 8: Qualitative evaluation of influence of uncertainties on the dietary exposure estimate

Sources of uncertainties	Direction[a]
Consumption data: different methodologies/representativeness/underreporting/misreporting/no portion size standard	+/–
Use of data from food consumption survey of a few days to estimate long-term (chronic) exposure for high percentiles (95th percentile)	+
Correspondence of reported use levels to the food items in the EFSA Comprehensive Food Consumption Database: uncertainties to which types of food the levels refer to	+/–
Food categories included in the exposure assessment: - the most relevant chocolates/confectionary selected assumed to contain the food additive - data not available for certain food categories which were excluded from the exposure estimates (only the liqueurs)	 + –
Concentration data: - levels considered applicable for all items within the entire food category	 +
Maximum level exposure assessment scenario: -food categories authorised at the highest level reported	 +
Refined exposure assessment scenarios: - exposure calculations based on one maximum and one mean levels (reported use from industries)	 +/–
Uncertainty in possible national differences in use levels of food categories	+/–

(a): +, uncertainty with potential to cause overestimation of exposure; –, uncertainty with potential to cause underestimation of exposure.

Overall, the Panel considered that the uncertainties identified would, in general, result in an overestimation of the exposure to silver (E 174) as a food additive in European countries for the refined scenario.

2.9.5. Dietary occurrence from sources other than the food additive

In a study conducted to determine the presence of trace elements in some seafood species, the levels of Ag detected were 0.030 ± 0.017 mg/kg in red mullet, 0.038 ± 0.024 mg/kg in grey mullet and 0.032 ± 0.029 mg/kg in green tiger prawns (Yarsan et al., 2014).

Following a call for data, the National Institute of Nutrition and Seafood Research (Documentation provided to EFSA No8) has reported silver total concentrations (mg/kg) in seafood and other food matrices. Most samples were from wild fish catches or aquaculture where silver was not present as food additive. The analyses were performed for several years from 2006 to 2011. From the 11,434 samples analysed, 7,842 were below the limit of quantification (LOQ). The mean levels found for some species are presented in Table 9. The Panel noted that the values were very low for some species as trout and rainbow trout, presenting a high standard deviation (data not shown).

Table 9: Silver concentration (mg/kg) in some species analysed during different periods.

SPECIES							
Oysters 2006-2011	1.049	Coalfish	0.024	Mackerel	0.023	Common whelk	0.027
Greenland halibut 2006-2011	0.006	European plaice 2007	0.005	Caplin 2007-2010	0.09	Scallop 2006-2011	0.027
Trout 2007-2009	-	Shrimp 2007-2010	0.185	Ling 2008	0.048	Cusk 2008	0.063
Rosefish 2007	0.074	Rainbow trout 2008	-	Salmon 2005-2011	0.72	Blue mussel 2006-2011	0.013
Cod 2005-2011	0.259	Polar cod 2006-2010	0.022	Halibut 2005-2008	0.045		
Soya	2.27	Spiny dogfish 2007-2008	-	Crab 2007-2010	0.465		

The 2nd French Total Diet Study (ANSES, 2011) estimated the intake of silver. Most of the analysed samples had a silver level below the limit of detection (LOD)/ LOQ (82%). The highest concentration levels were found in molluscs, crustaceans and offal. For adults, the mean exposure ranged from 1.29 µg/kg bw/day (lower bound) to 2.65 µg/kg bw/day (upper bound); at the 95th percentile, exposure levels ranged from 2.82 µg/kg bw/day (lower bound) to 4.78 µg/kg bw/day (upper bound). For children, the mean exposure ranged from 1.60 µg/kg bw/day (lower bound) to 3.47 µg/kg bw/day (upper bound); at the high exposure levels ranged from 3.60 µg/kg bw/day (lower bound) to 6.59 µg/kg bw/day (upper bound). Main contributors were molluscs and crustaceans for adults and milk and water for children.

2.9.6. Dietary exposure from all sources

The exposure from the food additive and the regular diet (ANSES, 2011) could lead to a mean intake for children around 3.5 µg/kg bw/day (non-brand-loyal scenario). On average, exposure from the food additive would represent around 30% of the total dietary exposure to silver.

3. Biological and toxicological data

The Panel was not provided with a newly submitted dossier and based its evaluation on previous evaluations and additional literature that became available since then. No new toxicological or biological information was submitted to the Panel for the re-evaluation of silver following EFSA public calls for data. The Panel noted that not all of the original studies on which previous evaluations were based were available for this re-evaluation.

The present opinion briefly summarises the major studies evaluated previously by the SCF (SCF, 1975) and JECFA (JECFA, 1977, 1978) in these evaluations and describes the additional studies in more detail.

Data on elemental silver are not available.

The Panel noted that AgNPs are released from confectionery pearls (Verleysen et al., 2015) and nanosilver is unstable and releases ions (see Section 2.5). The Panel was aware of the extensive database on ionic silver or AgNPs, however the relevance of these data to the evaluation of silver as a food additive (E 174) was not apparent. Therefore, the Panel considered these data could not be directly applied to the evaluation of the food additive.

In this opinion, only data with non-capped nanoparticles are included. However, when corresponding capped nanoparticles have been studied in the same experiments, also those data are included. References of the studies with capped material are given in Appendix C.

3.1. Absorption, distribution, metabolism and excretion (ADME)

The most important studies evaluated by JECFA (JECFA, 1977), as well as several additional studies identified in the literature search are summarised below.

3.1.1. Ionic silver

Studies evaluated by JECFA

Furchner et al. (1968) investigated the ADME of silver (^{110m} ionic silver, as the nitrate) in mouse, rat, monkey and dog following oral administration. Female RF mice (body weight 27 g, age 3 months, n = 12) were given 0.25 µCi; male Sprague–Dawley rats (body weight 360 g, age 3 months, n = 6) were given 0.5 µCi; male beagle dogs (body weight 13,300 g, age 90 months, n = 4) were given 0.6 µCi, and male *Macaca mulatta* monkeys (body weight 6,700 g, age 48 months, n=4) were given 0.6 µCi. Faeces and urine were collected. Animals were euthanised at various time points to assess the concentration–time profile of radioactivity in tissues. The following tissues were investigated: testis, brain, spleen, kidney, liver, heart, lung, intestine, fur, blood and carcass. Ninety per cent or more of oral applied radioactivity were excreted in the faeces. Cumulative excretion at day 2 was 99.6% for the mouse, 98.3% for the rat, 90.4% for the dog and 94.4% for the monkey. The urinary/faecal excretion ratios for ^{110m}ionic silver were 0.001 for the mouse, 0.001 for the rat, 0.025–0.061 for the dog and 0.019–0.258 for the monkey.

Ham and Tange (1972) found silver granules after given silver nitrate in the drinking water to be deposited in the rat glomerular basement membrane. Albino and hooded female rats (strain not specified; age not specified; body weight of 90–100 g; number of animals not specified exactly, but at least 26 per strain due to the study protocol were given a 0.25% solution of silver nitrate as drinking water (equivalent to 142 mg ionic silver/kg bw/day[20]). A pair of each of the rat strains was euthanised at 1, 2, 3, 4, 8 and 12 weeks. Silver nitrate administration was then withdrawn and all animals were given tap water. In addition, pairs of rats were euthanised at 1, 2, 3, 6, 10 months and four animals per strain were euthanised at 16 months. The kidney was investigated by microscopy and electron

[20] Calculated by the Panel according to EFSA Scientific Committee (2012).

microscopy. Moreover, the silver content in the liver and kidney was determined. Silver granules were found particularly in the glomerular basement membrane. After administration had been discontinued, silver granules in the basal membrane continued to increase in size as renal excretion of silver from the body continued. After some months the silver granules decreased in number and size and eventually disappeared. The silver content of the liver showed gradual decline after intake had ceased over the duration of the experiment.

Additional studies, not evaluated by JECFA

3.1.1.1. Mice

Wang et al. reported radioactivity (orally administered silver ions given as a tracer ^{105}ionic silver) to be located in the liver, heart, spleen, kidney, fur and muscle of mice (Wang et al., 2001).

Pelkonen et al. (2003) investigated the concentration time profile of radioactivity into different tissues when given in the drinking water [^{110m}Ag]Silver nitrate (0.03 mg silver/L, equivalent to 0.005 mg ionic silver/kg bw/day[21]) was given to five male outbred NIH/S mice (10–12 weeks old, body weight 23–26 g) for 1 or 2 weeks. Tissue distribution was analysed by gamma radioactivity. The highest concentrations were found in muscle, followed by cerebellum, spleen, duodenum and myocardial muscle and no accumulation was observed.

3.1.1.2. Rats

Dijkstra et al. (1996) administered silver ions as a water-soluble silver salt (80 nmol silver ions/100 g bw, 8.6 mg ionic silver/kg bw, salt not specified) intravenously to Wistar rats (body weight 260–300 g, age not specified, n=4) and collected the bile for 4 hours via an indwelling catheter in the bile duct in 30 min intervals. Biliary excretion of silver ions occurred; the recovery in bile was 48.5 and 23.2% of the dose in NW rats and in GY rats, respectively.

Distribution in several organs

Olcott (1948) has studied the tissue distribution of orally administered silver nitrate and silver chloride in rats (age starting shortly after weaning, n=2–3) given a 1:1000 dilution of the silver salts in about 1:300 sodium thiosulphate for their lifetime (equivalent to 32 and 38 mg ionic silver/kg bw/day for silver nitrate and silver chloride, respectively[21]). A range of organs were investigated. The eyes became progressively darker. The tongue, teeth and salivary glands were black. The thyroid was regularly grey to black on microscopic examination. The parathyroids contained deposition of moderate numbers of granules. The heart was grey at necropsy. The liver was slightly dark on gross examination. The pancreas was one of the most deeply pigmented parts of the body. Granules of silver were recognised in the brain tissue or in the vessels. The kidney was often very dark on gross examination. Dark spots were found in the glomerulus. Silver was deposited in the basement membrane of the glomerular tuft, lesser amounts of pigment were found in the basement membrane of the collecting tubules or in the wall of the small blood vessels.

Walker (1971) investigated the organ distribution of silver ions given in the drinking water. Male Sprague–Dawley rats (12/group, age 8 weeks, body weight not specified) were given silver nitrate at 6, 12 or 24 mM in the drinking water (equivalent to 59, 118 and 236 mg ionic silver/kg bw/day[21]). The 6 and 24 mM groups were discontinued after 12 and 2 weeks, respectively. The 12 mM group was dosed for 0, 2, 4, 6, 8, 10, 12, 16, 25 and 60 weeks; a series of six rats were given 12 mM for 10 weeks and were then restored to ordinary drinking water and euthanised at 2, 4, 6, 8, 10 and 12 weeks later (lag phase study). Kidney, skin, eye, liver and muscle were taken from some animals for electron microscopy. In addition, 20 organs or tissues were taken from each animal for light microscopy. By the macroscopic pathological investigations, it was observed that the animals had stained muzzle and teeth. Microscopic investigation showed the following: within 6 weeks of commencing

[21] Calculated by the Panel according to EFSA Scientific Committee (2012).

administration, sites where silver deposits were detected included the glomerulus, colon and liver. After a further 6 weeks, silver deposits were detected in choroid plexus, thyroid and skin appendage basement membranes. At 25 weeks of administration, silver was found in skin surface, urinary bladder and prostatic acinar membranes. In the lag phase study, it was found that deposition continued 4 weeks after discontinuation of silver administration.

Distribution in the kidney

Walker (1972) studied the renal content of silver given as silver nitrate in the drinking water. Sixteen male Sprague–Dawley rats (8 weeks of age, body weight not specified) were given silver nitrate for 0, 2, 4, 6, 8, 10, 12, 16, 25, 60 and 81 weeks at a concentration of 12 mM (equivalent to 118 mg ionic silver/kg bw/day[22]). Parts of renal cortex were processed for electron microscopy. Silver was found in the glomerular basement membrane as already described by Ham and Tange (1972).

Creasey and Moffat (1973) investigated the distribution of ingested silver in the rat kidney following administration of 0.15% silver nitrate in drinking water to weanling rats (strain and body weight not specified, n=26) for 4–15 weeks (equivalent to 85 mg ionic silver/kg bw/day[22]). Kidneys were subjected to light and electron microscopy. Granules containing silver that never exceeded 30 nm was found in the glomeruli, around the vascular bundles and capillaries of the outer medulla. In the inner medulla granules containing silver were found in the vasa recta, loops of Henle and in the interstitial cells and matrix.

Distribution in the spleen

Pereira (1977) investigated the localisation of silver in the rat spleen. Young male albino rats (strain, age, number of animals and body weight not specified) were given for many months (time period not specified further) drinking water with 1.5 g silver nitrate per litre (equivalent to 85 mg ionic silver/kg bw/day[22]). Following euthanisation, specimens were prepared for electron microscopy. Silver was found in several structures in the spleen, e.g. dense granules were found in the elastic membranes of the splenic capsule and trabeculae, and in discrete locations throughout the red pulp and marginal zone. In the red pulp, extremely dense granular deposits occurred in the basal laminae. Dense granules were also deposited in the macrophages, reticular fibres and marginal sinus basal laminae of the splenic marginal zone.

Distribution in the brain

Van Breemen and Clemente (1955) investigated the ability of silver ions to cross the blood–brain barrier. Rats (strain, age, number of animals and body weight not specified) were administered 0.5% silver nitrate in their drinking water for 6–8 months (equivalent to 158 mg ionic silver/kg bw/day[22]). The rats were euthanised and sections of the brain were examined by electron microscopy. Precipitated silver was found in the perivascular spaces of the choroid plexus and in the area postrema. Silver was specifically deposited on the outer surfaces of endothelial cells, on collagen fibrils of the stroma and on the vessel side of the cell membranes adjacent to perivascular spaces. Very little silver was found around the capillaries in the cerebrum, cerebellum and most of the medulla.

Rungby and Danscher (1983) investigated the distribution of silver in the brain by electron microscopy. Wistar and Sprague–Dawley rats of both sexes (10 animals/group, weighing at least 120 g) were administered silver nitrate and silver lactate at a concentration of 0.01% dissolved in the drinking water for 4 months (equivalent to 6 mg ionic silver/kg bw/day[22]). Silver nitrate in the drinking water resulted in silver deposition in several brain regions. Regarding cell types, a relatively high content of silver was found in glia with silver nitrate, whereas silver lactate resulted in deposition

[22] Calculated by the Panel according to EFSA Scientific Committee (2012).

preferentially in neurons. Silver was located intracellularly in the lysosomes and extra-cellularly in basement membranes and elastic fibres of the vessels.

Distribution in the eye

Rungby (1986) investigated the ultrastructural localisation of silver in the eyes. Male Wistar rats (body weight 120 g, 3 animals/group) were administered silver nitrate or silver lactate at a concentration of 0.02 % dissolved in the drinking water for 45 days (equivalent to 12 mg ionic silver/kg bw/day[22]). Silver was found in lysosomes of most cell types, with the exception being the neural retina. Extracellularly, silver was present in vascular basal laminae and in connection with connective tissue fibres.

Olcott (1947) also found pigmentation of the eyes following ingestion of silver nitrate. A total number of 159 rats (strain only specified as animals coming from Rockland Farms, New York City, N.Y.; 82 males, 55 females that had no litters and 22 females that had at least one litter; age at least 1 month; body weight not specified) had their eyes examined; 143 of the rats received a 1:1000 solution of silver nitrate whereas 16 rats received a 1:1000 solution of silver chloride held in solution by about 3.5 times as much sodium thiosulphate as the silver salt (equivalent to 32 mg ionic silver /kg bw/day[23]). Silver was given from the age of 1 month until death. Silver was found during life and at necropsy as pigmentation of the eyes. The amount of pigmentation was directly related to the duration of treatment.

Matuk et al. (1981) investigated the distribution of silver in rat eyes. Forty weanling male Wistar rats (age and body weight not specified) were administered a 0.25% silver nitrate solution via the drinking water for up to 8.5 months (equivalent to 81 mg ionic silver/kg bw/day[23]). After 10 weeks, two rats were euthanised and the eyes were processed for electron microscopy. The remaining rats were divided into two groups: 1) A group that continued with the same solution for the next 6 months and 2) a group that was shifted to water for 6 months. At monthly intervals, one rat from each group was euthanised and the eyes were examined for silver deposits by electron microscopy. Particles containing silver were found in the eyes of the rats. The number and size of these particles increased with continued ingestion of silver nitrate, but decreased when silver nitrate was withdrawn. However, fine particles of silver were still present 12 months after the end of silver nitrate ingestion.

The Panel noted that none of the reports indicated whether the granules/deposits found by electron microscopy represented silver in its inorganic form or silver bound to organic compounds, e.g. silver-glutathione.

Occurrence in milk

Ilyechova et al. (2012) reported that silver ions were present in the breast milk of rat dams receiving a dose of 50 mg silver chloride/kg bw/day from the diet, starting on the first day of lactation. This was indicated by a higher silver concentration in the breast tissue of silver-treated dams (4.7 µg/g tissue) than of controls (0.15 µg/g tissue). Also, the stomach of 10-day-old rats breastfed by silver-treated dams contained much more silver (35 µg/g tissue) than stomach from rats receiving milk from control dams (1 µg/g tissue). In this study, the authors also reported that silver ions were transported and accumulated in the liver of the pups and to a much less extent in their brain.

3.1.1.3. Human

The Panel was aware that there are many data reporting distribution of silver in various human organs following prolonged exposure to very high doses of silver in different forms (see Section 3.2.7.2).

[23] Calculated by the Panel according to EFSA Scientific Committee (2012).

3.1.2. AgNPs

Additional studies, not evaluated by JECFA

3.1.2.1 Silver ions from AgNPs in laboratory synthetic set-ups

Several studies have been reported in the literature on the behaviour of AgNPs in different environments. These studies have frequently been performed with citrate-stabilised or other forms of stabilised colloidal AgNPs in aqueous systems. Although considering that stabilised AgNPs are not representative of the food additive E 174, the Panel considered that these studies provide valuable information that can be useful as evidence of the release of silver ions from elemental AgNPs even if the rate of release could be presumably different considering the possible effect of the capping agent used. Some of these studies are reviewed below.

Liu and co-workers (Liu and Hurt, 2010; Liu et al., 2010, 2012) extensively investigated the behaviour of colloidal AgNPs in aqueous systems and in simulated biological environments. In the presence of oxygen, AgNPs were seen to undergo chemical conversion that can affect silver bioavailability and toxicity. Conversions were simulated and included accelerated oxidative dissolution in the simulated GI (GI) tract, thiol binding and exchange, photo-reduction in the near-skin regions of thiol- or protein-bound silver to secondary zerovalent AgNPs, and rapid reactions between silver surfaces and reduced selenium species (Liu et al., 2012). Some biological environments have low pH (e.g. gastric fluid) which facilitates silver dissolution as ionic silver. High concentrations of organic ligands (thiols) and relevant concentrations of selenium in addition to sulfur: both selenium and sulfur can yield silver precipitates, with Ag_2Se being more insoluble than Ag_2S. Similarly, under certain conditions the presence of the chloride ion Cl^- may determine ionic silver to precipitate as AgCl. Silver nanoparticulate surfaces can adsorb ionic silver, so that even simple colloids can be thought to contain three forms of silver: solid elemental silver, free ionic silver or its complexes, and surface-adsorbed ionic silver (Liu and Hurt, 2010).

The same authors developed a kinetic model to describe the observed release of ionic silver from AgNPs surfaces in the aqueous systems and biological environments utilised for the experimental observations (Liu et al., 2012). According to the model, the oxidative dissolution of AgNPs is strongly dependent on pH and particle size, in that dissolution rate was shown to increase with lowering pH and could be much higher for nanoparticles than for microparticles. The authors observed that although gastric fluids should lead to an accelerated dissolution of AgNPs, dissolution can be incomplete for most particles due to the limited residence time in stomach (10–240 min). The dissolution kinetics in laboratory aqueous media was modelled at different pH (ranging from 1.5 to 7.4) and with various particle sizes (Ø = 2–500 nm). The Panel noted that the study included microparticles and that at pH 1.5 (resembling the pH of the stomach), for short incubation times (< 3 h), ionic silver formation rate from 5-nm AgNPs was more than fivefold higher than that at pH 7.4 (resembling the pH of the blood). Small AgNPs (Ø < 20 nm) appeared to dissolve much quicker than larger nanoparticles (Ø > 20 nm). By comparison, 500 nm microparticles seemed to be almost unreactive. Surface area normalisation proved that the high dispersion of nanoparticles had a very strong impact on the formation rate of ionic silver.

Loza et al. (2014) investigated PVP-coated AgNPs dissolution in biological media and related-biological effects. It was observed that AgNPs (in the form of 70-nm-Ø spherical particles) released silver ions if oxidising species like molecular oxygen or hydrogen peroxide were present. The presence of a reducing sugar (glucose) had only a small effect on dissolution rate. In the presence of chloride ions, precipitation of silver chloride nanoparticles occurred (apparently, not on the surface of the initial AgNPs); at physiological salt concentrations, precipitation of silver chloride inhibited the precipitation of silver phosphate. When the AgNPs surface was passivated by cysteine, the dissolution was quantitatively inhibited. AgNPs were subject to an 8-month-long immersion in pure water at a neutral pH: a dissolution of only about 50% was observed (for which no sound explanation was found), and no surface changes were detected in the unreacted AgNPs by TEM. The authors also

carried out a literature survey on the dissolution of AgNPs: it ultimately showed that only qualitative trends could be identified from the available studies as the nature of the nanoparticles and of the immersion media were in general not comparable. Dissolution effects were confirmed by cell culture experiments (human mesenchymal stem cells and neutrophil granulocytes), where AgNPs that were stored under argon had a clearly lower cytotoxicity than those stored under air; they also led to a diminished formation of reactive oxygen species (ROS). This highlighted that silver ions can be released from AgNPs.

3.1.2.2 *In vitro* investigations of the absorption of AgNPs.

Several authors (Bouwmeester et al., 2011; Rogers et al., 2012; Walczak et al., 2012) explored the absorption of AgNPs using *in vitro* systems.

Bouwmeester and co-workers (Bouwmeester et al., 2011) used Caco-2 and M cells as an *in vitro* intestine model to study the passage of AgNPs and their ionic forms, and to assess their effects on whole-genome mRNA expression in the cells. The cells were exposed to AgNPs in four sizes (producer's TEM assessment: Ø = 20, 34, 61, and 113 nm) for 4 h. Exposure to silver ions was included as a control as 6–17% of the AgNPs silver content were found to be transformed into silver ions, the ion levels increasing with decreasing size of nanoparticles. The amount of silver ions that passed the Caco-2 cell barrier was equal after exposure to silver ions and for exposures with nanoparticles. AgNPs induced clear changes in gene expression in a range of stress responses including oxidative stress, endoplasmatic stress response and apoptosis. However, the gene expression response to AgNPs was very similar to that of $AgNO_3$. Translocation of nanoparticles through the epithelium depended on their physico-chemical properties such as size, surface charge, lipophilicity/hydrophilicity and presence/absence of a ligand. The study, carried out with nanoparticles selected in the range of 20–30 nm, indicated that the translocation of silver across the cell membrane in the model utilised was likely to occur as silver ions released from the nanoparticles and not as AgNPs as such. Similarly, the observed effects of the AgNPs were likely exerted by the silver ions that were released from the nanoparticles.

The absorption of silver from ingested AgNPs largely depends on initial particle size, shape and surface coating, properties which will influence particulate aggregation, solubility and chemical composition during transit in the GI tract. Rogers and co-workers (Rogers et al., 2012) used an *in vitro* model to expose citrate-stabilised AgNPs (Ø = 40 nm, nominal) to synthetic human stomach fluid (SSF) at pH 1.5; changes in size, shape, zeta potential, hydrodynamic diameter and chemical composition were determined during a 1-h exposure period by various analytical techniques. According to this experiment, ingested AgNPs may be converted to a variety of aggregated and chemically modified particles in the stomach. The authors acknowledged that, given the wide range of coating compounds that vary in chemical properties or surface charge, the reported results may not be representative of AgNPs preparations in general. Moreover, absorption of ionic silver from these Ag-containing materials will also depend on the interactions between this mixture of Ag-containing species and the absorptive surfaces of the GI tract.

Walczak et al. (2012) investigated the fate of AgNPs in a model mirroring GI digestion following oral ingestion. The study utilised 60-nm AgNPs and silver ions from $AgNO_3$. After exposure to saliva, gastric and intestinal fluid, samples were analysed with various analytical techniques. In the presence of proteins, after exposure to gastric fluid the number of particles dropped significantly, to rise back to original values. A reduction in number of particles was caused by clustering of particles in bigger particles, as revealed by analysis with SEM/EDX spectroscopy: some of the clusters contained AgNPs and chlorine. During exposure to intestinal fluid, these clusters broke back into single 60-nm AgNPs. The authors concluded that, under physiological conditions (i.e. in the presence of proteins), these AgNPs can reach the intestinal wall in their initial size and composition. It was also observed that exposure to intestinal fluid of $AgNO_3$ in the presence of proteins resulted in particle formation. These nanoparticles (Ø in the range of 20–30 nm) were composed of silver, sulfur and chlorine. On the

whole, ingestion of both AgNPs and silver ions ultimately appeared to lead to intestinal exposure to particles, although with a different chemical composition.

The Panel noted that the findings from the above *in vitro* studies allow to draw the conclusion that the transepithelial transport occurs with a similar efficiency for AgNPs as for silver ions suggesting that silver ions are absorbed. This in accordance with the report of the Danish Environmental Protection Agency (DTU, 2013), dealing with the systemic absorption of ingested nanomaterials, which pointed out that the results suggest that AgNPs dissolve in the GI tract prior to intestinal absorption, to enter circulation and subsequently reach primarily the liver and spleen and to a lesser degree other organs.

3.1.2.3 Mice

Park et al. (2010) investigated the tissue distribution of silver in mice following oral administration of a suspension of AgNPs (22, 42 and 71 nm in diameter) and silver from microsized particles (323 nm in diameter). ICR mice (5/group – both sexes but the number of animals per sex not specified, 6 weeks of age, weight not specified) were administered the AgNPs by gavage (vehicle: deionised water) in a dose of 1 mg/kg bw/day for 14 days. The control group received deionised water prepared by the same process to prepare the AgNPs suspension. The silver ion concentration in brain, lung, liver, kidney and testes was measured using ICP-MS after tissue digestion. Silver, measured by ICP-MS after solving the tissues in 70% HNO_3 and treatment with 30% H_2O_2, was found in all the tissues of animals dosed with nanoparticles, except in testes of animals which had received the 71 nm AgNPs. The concentrations were dependent on the particle diameter with lower concentrations in the tissues of animals treated with NP of higher diameter. In contrast to the findings after administration of AgNPs (22–71 nm), there was no silver found in the tissues following administration of microsized silver particles (323 nm).

3.1.2.4 Rats

Van der Zande et al. (2012) investigated the distribution and elimination of AgNPs and silver ions in rats. Male Sprague–Dawley rats (5/group, 6 weeks old, body weight about 245 g) were exposed daily by oral gavage for 28 days to 90 mg/kg bw of AgNPs (18 nm, non-coated or 12 nm, PVP-coated, in diameter) or 9 mg/kg bw of silver nitrate (corresponding to 6 mg ionic silver /kg bw/day). Included were also wash-out groups identically exposed to silver but not sacrificed until day 36 or day 84. At the end of the 4-week treatment, total silver contents were determined with atomic absorption spectrophotometry in a broad range of organs, blood and intestinal contents. Furthermore, SP-ICP-MS was applied to detect silver containing nanoparticles in a selection of these organs and in intestinal contents. Silver was found in all examined organs (liver, spleen, testis, kidney, brain, lung, blood, bladder and heart) with the highest levels in the liver and spleen for all silver treatments. Silver concentrations in the organs were highly correlated with the amount of silver ions in the silver nanoparticle suspensions, indicating, according to the authors, that mainly silver ions passed the intestines in the silver nanoparticle exposed rats. In all groups (the two nanoparticle groups, as well as the silver nitrate group), silver was cleared from most organs after 8 weeks of wash out. However, silver content persisted for the observation period in the brain and in the testis. There were no significant differences in distribution profiles between silver nitrate and the two types of AgNPs.

In a 28-day study by Kim et al. (2008) (performed according to the OECD TG 407) on AgNPs in Sprague–Dawley rats (10/sex/group, 6 weeks old, mean body weight 283 g for males and 192 g for females) were administered 0, 30, 300 and 1,000 mg/kg bw/day AgNPs (diameter of 60 nm, coating not specified) by gavage (vehicle: 0.5% carboxy methyl cellulose) for 28 days. At the end of the 4-week treatment, tissue silver was determined by atomic absorption spectrophotometry. A dose-dependent content of silver was found in all examined tissues ($p < 0.05$ or < 0.01) including the testis, kidney, liver, brain, lung, stomach and blood.

Kim et al. (2010) also performed a 13-week study (according to the OECD TG 408) on AgNPs in Fisher 344 rats (10/sex/group, 5 weeks of age, mean body weight of males and females were

approximately 100 and 90 g, respectively). Rats were administered 0, 30, 125 and 500 mg/kg bw/day AgNPs (diameter of 56 nm, coating not specified) by gavage (vehicle: 0.5% carboxy methyl cellulose). At the end of the 90-day treatment, tissue silver was determined by atomic absorption spectrophotometry. A dose-dependent content of silver was found in all tissues examined including testis, liver, kidney, brain, lung and blood. A gender difference was observed for kidneys where a twofold higher concentration of silver was observed in the kidneys of females as compared to males.

Summary

Upon oral exposure of animals to ionic silver or AgNPs, silver is systemically available. Silver concentrations in the organs were highly correlated to the size of the nanoparticles showing higher concentrations in animals treated with nanoparticles with a smaller diameter and to the amount of silver ions in the suspension of AgNPs. Bioavailability seems to be in the range of 2–20% depending on a range of factors including the animal species.

However, the Panel noted that, due to the many variables involved, the conversion rate of metal silver from nanoparticles to silver ions in biological systems is unknown. Moreover, the formation of ROS from the fraction of AgNPs which may be present in the food additive has not been determined. The rate of both processes depends on the size of particles and their relative surface.

Silver is distributed into all organs and tissues (mainly in the liver). Silver is also distributed into the brain following oral exposure, which is in contrast to the conclusions from the authors of studies from the 50s with silver nitrate or lactate, that silver would not cross the blood–brain barrier (van Breemen and Clemente,1955). However, in the more recent studies, it is also unclear whether silver is present in the brain endothelial cells or in the brain tissue. Silver ions were also detected in the milk of rat dams receiving a daily oral administration of silver chloride, and in the liver and in the brain of the pups. In rodents, silver is primarily excreted via the bile and faeces, but a small amount is also excreted via the urine.

The Panel noted that only one study described the fate of microsized silver particles in animals (Park et al., 2010). In this study, no silver was detected in any of the tissues of mice given an oral administration of microsized silver particles (323 nm), whereas silver was present in tissues of mice receiving a similar administration of nanosized silver particles (21 to 71 nm), indicating the impact of particle size on the conversion into silver ions of metallic silver, given in particulate form.

3.2. Toxicological data

No studies were reported on elemental silver.

3.2.1. Acute oral toxicity

No data were submitted to EFSA following a public call for data. The only oral acute toxicity study evaluated by JECFA (JECFA, 1977), as well as additional studies identified in the literature search are summarised below.

Studies evaluated by JECFA

Ionic silver

In mice, an oral dose of silver nitrate of 50 mg/kg bw (corresponding to 32 mg ionic silver/kg bw) caused death in 50% of the animals within the 14-day observation period (JECFA, 1977).

Additional studies, not evaluated by JECFA

3.2.1.1 Mice

Ionic silver / AgNPs

Cha et al. (2008) compared the acute response of mice livers to nano- or microsized silver particles. A silver nanoparticle solution was prepared based on the reduction in $AgNO_3$ with $NaBH_4$. Male balb/c mice (7-week old) were given a single dose of 2.5 g nanosized silver particles (13 nm; or microsized silver particles (2–3.5 μm) by gavage. Three days later animals were euthanised and livers were processed for microscopy. Both groups exhibited lymphocyte infiltration.

AgNPs

Maneewattanapinyo et al. (2011) showed that spherical AgNPs (with a particle diameter of 10–20 nm) at a limited dose of 5,000 mg/kg bw led neither to mortality nor acute toxic signs in ICR mice in an acute oral toxicity study performed according to the OECD TG 425 (Acute oral toxicity test: the up and down procedure). The AgNPs were synthesised preparing an aqueous solution of AgNO3 with a reducing agent (NaBH4), the AgNPs were purified by centrifugation, washed and adjusted to the initial volume with water. The solutions were diluted with distilled water to obtain different concentrations of AgNPs prior to use in the experiments.

3.2.1.2 Rats

Ionic silver

Tamimi et al. (1998) investigated the acute toxicity of an antismoking mouthwash with the active ingredient being 0.5% silver nitrate. Fischer 344 rats (10/sex, 10–12 months old, body weight 200–250 g) received 1 ml by gavage of either 200, 300 or 400 mg silver nitrate/kg bw of the mouthwash (corresponding to 126, 189 and 256 mg ionic silver/kg bw); the control group received the placebo (not further specified). Animals were observed for 2 weeks, dead animals were subjected to post-mortem examinations immediately after death. The oral LD_{50} values were 428 and 433 mg silver nitrate/kg bw for male and female rats, respectively (corresponding to 280 mg ionic silver/kg bw).

3.2.1.3 Rabbits

Ionic silver

Tamimi et al. (1998) investigated the acute toxicity of an antismoking mouthwash with the active ingredient being 0.5% silver nitrate. Californian rabbits (10/sex, 8–10 months old, body weight 1–1.2 kg) received 10 ml orally by gavage of either 200, 800, 1,000, 1,800 or 4,000 mg silver nitrate/ kg bw of the mouthwash (corresponding to 126, 504, 630, 1,134 or 2,520 mg ionic silver/kg bw); the control group received the placebo (not further specified). The animals were observed for 2 weeks and deceased animals were subjected to post-mortem examinations. The oral LD_{50} values were 1,261 and 1,320 mg/kg bw for male and female rabbits, respectively (corresponding to 794 and 832 mg ionic silver/kg bw).

Overall, oral LD_{50} values of approximately 32, 280 and 800 mg ionic silver/kg bw have been reported for silver nitrate in mice, rats and rabbits, respectively (Tamimi et al., 1998). For AgNPs (10–20 nm), a dose of 5,000 mg/kg bw did not lead to mortality or acute toxic signs in mice (Maneewattanapinyo et al., 2011).

3.2.2. Short-term and subchronic toxicity

No data were submitted to EFSA following a public call for data. In general, the studies in rats evaluated by JECFA (JECFA, 1977) are special purpose studies investigating, for example, the effect of silver acetate in vitamin E-deficient rats or supplementation with essential vitamins and/or minerals; these studies are not considered of relevance for the evaluation of silver as a food additive. Two studies evaluated by JECFA (JECFA, 1977) have been performed in poultry (chicks and turkey poults); these studies are not considered of relevance for the evaluation of silver as a food additive. The remaining two studies evaluated by JECFA (JECFA, 1977) were described in Section 3.2.7 Other studies.

Additional studies, not evaluated by JECFA

3.2.2.1 Mice

AgNPs

Park et al. (2010) investigated the inflammatory response in mice following oral administration of AgNPs (22, 42 and 71 nm in diameter) and silver from microsized particles (323 nm in diameter). The commercial AgNPs were suspended with sonication in tetrahydrofuran (THF) that was evaporated by adding deionised water to the same volume as THF. After the AgNPs, suspension was filtered through different pore sizes and the particle size analysed finding the following average diameters 22, 42, 71 and 323 nm, respectively. THF was completely absent in the final suspension of nanoparticles.

The study consisted of two parts. In the first part, ICR mice (5/group – both sexes but the number of animals per sex not specified, 6 weeks of age, weight not specified) were orally administered the AgNPs by gavage (vehicle: deionised water) at 1 mg/kg bw/day for 14 days. In the second part, ICR mice (6/group – both sexes but the number of animals per sex not specified, 6 weeks of age, weight not specified) were orally administered the AgNPs (42 nm in diameter) by gavage (vehicle: deionised water) at 0.25, 0.5 or 1 mg/kg bw/day for 28 days. The control group in both parts received deionised water prepared by the same process to prepare the AgNPs suspension. In the 14-day study, no changes were observed in body weights, relative organ weights (liver, kidneys, testis, brain and lung) or histopathology (liver, kidney and intestines) in all groups of mice treated with AgNPs (1 mg/kg bw/day). In the 28-day study, the serum levels of alkaline phosphatase (ALP) and aspartate transaminase (AST) were significantly increased ($p < 0.01$) in both sexes administered 1 mg/kg bw/day, and the level of alanine transaminase (ALT) was significantly increased ($p < 0.01$) in females administered 1 mg/kg bw/day. The histopathological examination revealed a slight inflammatory cell infiltration in the kidney cortex in both male and female mice (incidences not reported). According to the authors, the results of the two studies indicated that repeated oral administration of AgNPs may cause organ toxicity in mice and that the AgNPs (22, 42, 71 nm in diameter) are more active than the silver particles of 323 nm in diameter. As the histopathological kidney changes are minimal and the increase in the levels of ALP and AST are not accompanied by histopathological changes in the liver, the Panel considered these lesions of doubtful, if any, toxicological relevance.

3.2.2.2 Rats

Ionic silver

In rats (sex and number not further specified) given silver nitrate or silver chloride in suspension by sodium thiosulfate at a concentration of 1:1000 in the drinking water over long periods (equivalent to 57 and 68 mg ionic silver/kg bw/day for silver nitrate and silver chloride, respectively[24]) hypertrophy of the left ventricle was reported, which, according to the author, is presumed to indicate vascular hypertension that may have been due to the deposition of silver in the basement membranes of the renal glomeruli (Olcott, 1950). The study could not be used for risk assessment as the reporting was limited.

Walker (1971) investigated the effects of silver given in the drinking water. Male Sprague–Dawley rats (12/group, body weight not specified) were given silver nitrate at 6, 12 or 24 mM in the drinking water (equivalent to 59, 118 and 236 mg ionic silver/kg bw/day[24]). The 6 and 24 mM groups were discontinued after 12 and 2 weeks, respectively. The 12 mM group was dosed for 0, 2, 4, 6, 8, 10, 12, 16, 25 and 60 weeks; a series of six rats were given 12 mM for 10 weeks and were then restored to ordinary drinking water and euthanised at 2, 4, 6, 8, 10 and 12 weeks later (lag phase study). In addition, six rats were kept continuously at 12 mM to observe long-term toxicity. The kidney, skin, eye, liver and muscle were taken from some animals for electron microscopy. In addition, 20 organs or tissues were taken from each animal for light microscopy. Rats given 6 mM silver nitrate rapidly

[24] Calculated by the Panel according to EFSA Scientific Committee (2012).

developed brown-stained muzzles and teeth, but otherwise did not display any effects and were therefore only exposed for 12 weeks. Rats given 24 mM silver nitrate had an initial precipitous decrease in water intake, which rose slightly over the next 5 days and 3 out of 12 rats died. The rest of the animals were poorly groomed, listless and still drinking little, and therefore the study was discontinued in week 2. Animals given 12 mM silver nitrate drank less than controls at the beginning of the study, but returned to the control levels by 5 days. These animals had stained muzzles and teeth, and a slight depression in body weight. No other signs of toxicity were observed for up to 60 weeks. The long-term toxicity group showed a rapid deterioration in their clinical appearance at weeks 76–81; five of these rats recovered slowly upon return to normal drinking water.

AgNPs

In a 28-day study (performed according to the OECD TG 407) on colloidal AgNPs in Sprague–Dawley rats (10/sex/group, 6 weeks old, body weight not properly specified) were administered 0, 30, 300 and 1,000 mg/kg bw/day AgNPs (diameter of 60 nm) by gavage (vehicle: 0.5% carboxy methyl cellulose) (Kim et al., 2008). ALP was increased for male rats in the 300 and 1,000 mg/kg bw/day groups, for female rats only in the high-dose group ($p < 0.01$). Cholesterol was increased in male and female rats in the 1,000 mg/kg bw/day group ($p < 0.01$). Red blood cell count, haemoglobin and haematocrit were increased in female rats in the 300 and 1,000 mg/kg bw/day groups ($p < 0.05$ or < 0.01). Mean corpuscular volume was increased in males at 1,000 mg/kg bw/day ($p < 0.05$). The histopathological examination of the livers showed increased incidences of bile duct hyperplasia around the central vein to the hepatic lobule (dose dependently according to the authors) with infiltration of inflammatory cells, including eosinophils, in the hepatic lobule and in the portal tract. In addition, dilated central veins with infiltration of inflammatory cells were reported in and beneath the central veins (no details or incidences presented in the publication). The authors concluded that exposure to 300 mg AgNPs/kg bw/day and higher may result in slight liver damage. The Panel agreed with that conclusion.

Jeong et al. conducted a histochemical study of intestinal mucins of the rats of the study of Kim et al. 2008 described above. A dose dependent increase in silver nanoparticle accumulation was found in the small and large intestine lamina propria. Silver nanoparticle treated rats displayed increased higher numbers of goblet cells that had released their mucus granules as compared to the controls. The authors suggested that AgNPs induce discharge of mucus granules and abnormal mucus composition in goblet cells (Jeong et al., 2010).

Hadrup et al. (2012a) investigated the toxic potential of AgNPs and ionic silver in rats. Female Wistar rats (4 weeks old) were administered vehicle control, silver acetate (9 mg ionic silver/kg bw/day), or AgNPs (14 nm in diameter; PVP-coated) at 2.25, 4.5 or 9 mg/kg bw/day by gavage for 28 days; males were only given the vehicle control and 9 mg/kg bw/day AgNPs for 28 days. Body weight, macroscopic and microscopic pathology and a range of biochemical and haematological parameters were investigated. In addition, ionic silver led to decreased body weight gain ($p < 0.01$), decreased relative thymus weight ($p < 0.05$), increased plasma ALP ($p < 0.05$) and decreased plasma urea ($p < 0.05$). AgNPs at 9 mg/kg bw/day increased the haematocrit. Both ionic and nanoparticulate silver increased urine uric acid (only statistically significantly for AgNPs $p < 0.001$) and allantoin urine concentration ($p < 0.01$ and 0.001). In an accompanying *in vitro* investigation, AgNPs, ionic silver (silver acetate) and a 12-kDa-filtered subnano silver particle fraction were used to investigate cell death mechanisms in neuronal-like cells; the effect of subnano silver in the silver nanoparticle preparations strongly suggested that the toxic effects of AgNPs were mediated by free ions as toxic effects *in vitro* on viability (including apoptosis) could be explained by the subnano fraction and ionic silver.

Kim et al. (2010) performed a 13-week study (according to the OECD TG 408) on AgNPs in Fischer 344 rats (10/sex/group, 5 weeks of age, mean body weight of males was approximately 100 g, mean body weight of females was approximately 90 g). Rats were administered AgNPs (diameter of 56 nm)

at doses of 0, 30, 125 and 500 mg/kg bw/day by gavage (vehicle: 0.5% carboxy methyl cellulose). Body weight was decreased in high-dose male rats. ALP was increased in females at 500 mg/kg bw/day ($p < 0.01$). A decrease in serum magnesium was found for females at 125 and 500 mg/kg bw/day ($p < 0.01$). A decrease in serum inorganic phosphorus was found for females at 125 and 500 mg/kg bw/day (both with $p < 0.05$). Increased cholesterol was observed for both sexes (for males from 125 mg/kg bw/day, for females only at 500 mg/kg bw/day ($p < 0.01$)). No significant changes in the haematological parameters were noted except for a decreased reticulocyte counts for female rats at 30 mg/ kg bw/day ($p < 0.05$). The histopathological examination of the liver revealed minimal bile duct hyperplasia in 0/10; 4/10; 5/10 and 4/10 of the control, low, mid, and high-dose male rats, respectively and 0/10; 2/10; 2/10 and 2/10 of the control, low, mid and high-dose female rats, respectively. According to the authors, the higher incidence of minimal bile duct hyperplasia, with or without minimal necrosis or fibrosis suggests a treatment-related effect. As these histopathological liver changes are minimal and do not demonstrate a dose-effect relationship, the Panel considered these lesions of doubtful, if any, toxicological relevance.

Summary

Rats given 12 mM silver nitrate in drinking water (118 mg ionic silver/kg bw/day) for 0, 2, 4, 6, 8, 10, 12, 16, 25 and 60 weeks drank less than controls at the beginning of the study, but returned to the control levels by 5 days (Walker 1971). These animals had stained muzzles and teeth and a slight depression in body weight. Hadrup et al. (2012a) observed in rats after oral administration by gavage of silver acetate (9 mg ionic silver/kg bw/day) for 28 days, a decreased body weight gain, decreased thymus weight and increased liver enzymes and decreased plasma urea and allantoin urine concentration. In mice, repeated oral administration of AgNPs (22, 42, 71 nm in diameter, at 1 mg/kg bw/day for 14 days; or 42 nm in diameter, from 0.25 mg/kg bw/day for 28 days) induced effects on liver enzymes. However, no lesions in the liver were observed. Larger silver particles (323 nm in diameter, at 1 mg/kg bw/day for 14 days) did not induce any changes (Park et al., 2010).

In rats, colloidal AgNPs (diameter of 55–60 nm) resulted in slight liver damage (affected enzymes after 28 days at a dose of 300 mg/kg bw/day (Kim et al., 2008) and after 90 days at a dose of 125 mg/kg bw/day (Kim et al., 2010)). No effects were observed at 30 mg/kg bw/day. According to Kim et al. (2008, 2010), the bile duct hyperplasia observed in the liver in the 90-day study may point to a treatment-related effect of AgNPs. The Panel did not agree with this preliminary conclusion, and considered further research needed.

3.2.3. Genotoxicity

No data were submitted to EFSA following public calls for data. The only study evaluated by JECFA (JECFA, 1977), as well as additional studies identified in the literature search are summarised below.

3.2.3.1 *In vitro* studies

Study evaluated by JECFA

Ionic silver

No genotoxic activity of silver chloride was observed in a rec assay using *Bacillus subtilis* strains H17 and M45 (Nishioka, 1975). The Panel noted that this test system has not been validated and considered this study not relevant for risk assessment.

Additional studies, not evaluated by JECFA

Ionic silver

Eliopoulos and Mourelatos (1998) evaluated a suspension of silver iodide (AgI) in polyacrylamide in the Ames test at concentrations from 10 to 150 µg/mL using *Salmonella* Typhimurium strains TA1535, TA102, TA97 and TA98 with and without metabolic activation. No dose-related increase in

revertants was induced by treatment with AgI. A doubling effect on revertants was only observed with 30 µg/mL in TA102 without metabolic activation and at 150 µg/mL in TA97 with metabolic activation, doses which, according to the authors, appear to be nearly toxic for bacteria. Overall, the results of this study are considered negative.

Eliopoulos and Mourelatos (1998) also evaluated AgI, either dissolved in acetone or suspended in polyacrylamide, for the ability to induce sister chromatid exchanges (SCEs) in human cultured lymphocytes *in vitro* at concentrations of 2.3–1,000 ng/mL (acetone solution) or 5–10,000 ng/mL (suspension in polyacrylamide). AgI induced a doubling of SCEs at and above 100 ng/mL when dissolved in acetone, and at and above 1,000 ng/mL when suspended in polyacrilamide.

Foldbjerg et al. (2011) investigated the effects of $AgNO_3$ in the human alveolar cell line A549. Dose-dependent cellular toxicity caused by ionic silver (0.25–10 µg/mL) was demonstrated by the methyltetrazolium (MTT) and annexin V/propidium iodide assays. Treatment with $AgNO_3$ also induced dose-related mitochondrial damage, intracellular ROS and genotoxicity detected as an increase in bulky DNA adducts by ^{32}P postlabelling. Both cytotoxicity and genotoxicity of ionic silver were greatly decreased by pretreatment with the antioxidant *N*-acetyl-cysteine. The Panel noted that the bulky adducts detected showed a similar migration pattern in treated and untreated cells and accumulated in age-dependent way, and that according to the authors such adducts (I-compounds) 'appear to arise via the interaction of DNA with endogenous reactants formed in the course of metabolism, e.g. ROS'.

AgNPs

Ahamed et al. (2008) examined the DNA damage response to AgNPs (diameter 25 nm) in mouse embryonic stem (mES) cells and mouse embryonic fibroblasts (MEF). Exposure of cells to AgNPs (at final concentration of 50 µg/mL) for 4–72 h upregulated p53, the DNA damage repair proteins Rad51 and induced phosphorylation of the histone H2AX and cell death as measured by the annexin V and MTT assays.

Kawata et al. (2009) evaluated the *in vitro* toxicity of AgNPs (7–10 nm) at non-cytotoxic doses (0.1–3.0 mg/L, for 24 h) in human hepatoma cell line, HepG2, based on cell viability assay, micronucleus test and DNA microarray analysis. Silver carbonate (Ag_2CO_3) was also tested to compare the toxic effects of ionic silver and AgNPs. The cell viability assay demonstrated that AgNPs saccelerated cell proliferation at low doses (< 0.5 mg/L), which was supported by the DNA microarray analysis showing significant induction of genes associated with cell cycle progression. At higher doses (> 1.0 mg/L), only AgNPs induced abnormal cellular morphology and increased the frequency of micronucleus formation (up to 47.9 ± 3.2% of binucleated cells), indicating that AgNPs can elicit a much stronger chromosome damage than ionic silver. Cysteine, a strong ionic silver ligand, only partially abolished the formation of micronuclei (MN) mediated by AgNPs, indicating that ionic silver derived from AgNPs could not fully explain the genotoxic activity of AgNPs.

Kim et al. (2010) evaluated the *in vitro* cytotoxicity and genotoxicity of AgNPs (≤ 100 nm) using the trypan blue exclusion assay, the mouse lymphoma thymidine kinase (tk+/-) gene mutation assay (MLA) and the alkaline comet assay in L5178Y mouse lymphoma and BEAS-2B cells. In both cell types, AgNPs were weakly cytotoxic, with IC20 (20% inhibitory concentration) values > 3.7 and 1.7 mg/mL, respectively. Mutant frequencies in nanosilver-treated L5178Y cells (313–2,500 µg/mL) were slightly but not significantly increased compared to the vehicle controls, with and without S-9. In the comet assay (190–3770 µg(mL), significantly increased tail moment were observed in both L5178Y BEAS-2B cells after treatment with AgNPs, with and without S9, indicating that AgNPs can cause primary DNA damage and cytotoxicity, but not mutagenicity, in cultured mammalian cells.

Hackenberg et al. (2011) evaluated AgNPs (< 50 nm) induced DNA damage, cell death and functional impairment in human mesenchymal stem cells (hMSCs). hMSCs were exposed to AgNPs (0.01, 0.1, 1

and 10 µg/mL) for 1, 3 and 24 h. Cytotoxicity was measured by the trypan blue exclusion test and the fluorescein-diacetate test, DNA damage was evaluated by the alkaline comet assay and chromosomal aberration test. Cytokine release of IL-6, IL-8 and vascular endothelial growth factor (VEGF) was detected by ELISA. TEM revealed AgNPs distribution to cytoplasm and nucleus. Cytotoxic effects were seen at concentrations of 10 µg/mL for all test exposure periods. Both comet assay and chromosomal aberration test showed DNA damage after treatment with AgNPs at 0.1 µg/mL and above. A significant increase in IL-6, IL-8 and VEGF release indicated hMSC activation.

Park et al. (2011) investigated potential genotoxicity of AgNPs in a mouse embryonic fibroblasts cell line harbouring a plasmid containing the bacterial *lacZ* reporter gene (MEF-*lacZ*). AgNPs of average nominal diameters of 20, 80 or 113 nm were characterised by TEM analysis and dynamic light scattering (DLS) analysis. However, the results of TEM and DLS analysis were not reported and therefore the actual particle sizes used in the assay is unknown. Particles of the three nominal diameters were mixed with mouse embryonic fibroblast-lacZ cells at concentrations ranging from 0.1 to 50 µg/mL, after treatment DNA extracts, plasmid rescued and the mutation frequency was determined by transfecting plasmids in a competent lacZ deficient *Escherichia coli* strain. No induction in mutation frequency was observed. The Panel noted that this test system has not been validated for hazard identification and that no positive control was included in the study. Consequently, it is not possible to evaluate the sensitivity of the test method applied and the result reported in this study cannot be considered for risk assessment.

Asare et al. (2012) examined the cytotoxic and genotoxic effects of silver particles (12.5, 50 and 100 µg/mL) of nano- (20 nm) and submicron- (200 nm) sized in human testicular embryonic carcinoma cell line (NT2), and primary testicular cells from C57BL6 mice of wild type (WT) and 8-oxoguanine DNA glycosylase knock-out (mOgg1−/−) genotype. The results indicate that both silver nano- and submicron-particles are cytotoxic and cytostatic, causing apoptosis, necrosis and decreased proliferation in a concentration- and time-dependent manner. The 200 nm silver particles, and to a lower extent the 20 nm AgNPs, appeared to cause a concentration-dependent increase in DNA-strand breaks in NT2 cells, whereas this response did not seem to occur in mouse primary testicular cells.

Flower et al. (2012) evaluated the genotoxicity of spherical AgNPs (40–60 nm) in human peripheral blood cells using the alkaline comet assay. Results indicated that AgNPs (50 and 100 µg/mL) caused DNA damage following a 3 h treatment. A significant positive response was also elicited by short-time (5 min) treatment.

Li et al. (2012) investigated the mutagenicity of AgNPs (5 nm in diameter) in the Ames assay at concentrations from 0.15–76.8 µg/plate using *Salmonella* Typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 without metabolic activation. The test was performed according to OECD TG 471 using the pre-incubation method. No increases in mutant frequency over the vehicle control were found in the range of concentrations that could be assayed (2.4–38.4 µg/plate) due to toxicity.

Li et al. (2012) also investigated the genotoxicity of AgNPs (5 nm in diameter) in the *in vitro* micronucleus assay using human lymphoblastoid TK6 cells at concentrations from 10–30 µg/mL. The micronucleus frequency was increased in a dose-dependent manner. At the highest concentration (30 µg/mL the AgNPs induced a significant 3.17-fold increase (with a net increase in 1.60% in micronucleus frequency over the vehicle control), which, according to the criteria of the authors, was a weak positive response.

Ghosh et al. (2012) investigated the genotoxicity of AgNPs in human lymphocytes. AgNPs were characterised by TEM and SEM analysis and the particles in suspension was measured by DLS analysis. The TEM and SEM images revealed average sizes of 125 and 120 nm, respectively. The DLS analysis showed a maximum peak between 420 and 440 nm. The particles were tested in lymphocytes isolated from human blood at concentrations ranging from 25 to 200 µg/mL. DNA

damage was evaluated by comet assay. The results did not show a concentration-related increase. The highest increase was observed at the lowest concentration ($p < 0.05$) and significant increases were also observed at 50 and 200 µg/mL ($p < 0.05$). However, at 100 and 150 µg/mL significant increases were not observed.

Mei et al. (2012) investigated the effect of AgNPs on the mutation rate in mouse lymphoma cells. AgNPs were characterised by TEM analysis and DLS analysis. TEM analysis showed that 66% of the nanoparticles had diameters in the range of 4–8 nm, 24% in the range of 8–12 nm and 6% were above 12 nm. DLS analysis showed agglomerates sizes of particles ranging from 61 nm in water to 1,609 nm in Fischer's cell culture medium. The nanoparticles were added to the L5178Y/$Tk^{+/-}$ mouse lymphoma cell line in concentrations ranging from 3 to 6 µg/mL. Cytotoxicity investigations in a range finding experiment showed that at 3 µg/mL minor cytotoxicity occurred, whereas concentrations higher than 6 µg/mL induced moderate cytotoxicity. To investigate the genotoxicity, the mouse lymphoma forward mutation $Tk^{+/-}$ assay and the comet assay (both with and without the lesion-specific endonucleases) were performed. Treatments of L5178Y/$Tk^{+/-}$ mouse lymphoma cells resulted in a significant yield of mutants at concentrations between 3 and 6 µg/mL. Molecular analysis of induced mutants displayed both in small and large mutant colonies that mutant phenotype was associated with partial loss of heterozygosity of chromosome 11, suggestive of induced structural chromosome damage. In the comet assay, statistically effects ($p < 0.01$) were only observed in the presence of the lesion-specific endonucleases (at 4.5 µg/mL and above). Treatment with AgNPs also proved to modify the expression of genes involved in the production of ROS, oxidative stress, antioxidants and DNA repair, suggesting that the observed genotoxic effects were due to AgNPs-induced oxidative stress.

Li et al. (2013) investigated the genotoxic effect of AgNPs in primary Syrian hamster embryo cells. AgNPs dissolved in cell culture media determined by DLS analysis showed a hydrodynamic size distribution with a peak at 100 nm and 69% of the number concentration was below 100 nm. Cytotoxicity was determined by the MTT assay. A reduction in cell viability was observed between 25 and 67% in the concentration range 2.5–40 µg/mL. The genotoxic potential was investigated using a cytokinesis-block micronucleus assay. Syrian Hamster Embryo cells were tested in two concentrations of 20 or 40 µg/mL. Statistically significant ($p < 0.001$) increases in MN were recorded for both concentrations.

Kim et al. (2013) investigated the genotoxic effect of AgNPs in Ames test, by comet assay and by the micronucleus assay in Chinese hamster ovary cells. The particles were characterised by SEM, TEM and the hydrodynamic size distribution of the particles in aqueous suspension was determined with DLS analysis. In scanning electron microscopy (SEM) and TEM, the single particle size was 100 nm or less. The DLS analysis showed that about 50% of the particles were in the range of 40–59 nm. In the *Salmonella* Typhimurium assay the strains TA98, TA100, TA1535 and TA1537 were used at concentrations ranging from 100 to 500 µg/plate, with or without rat S9 liver fraction. No effects were observed in the Ames test. Comet assay and micronucleus assay were conducted in Chinese hamster ovary cells with concentrations ranging from 0.01 to 10 µg/mL. Cytotoxicity measurements were not conducted in connection with the comet assay. Therefore, the cytotoxicity is unknown of the concentrations applied in the comet assay. AgNPs induced (statistical significant, $p < 0.01$) DNA damage at all concentrations tested. Micronucleus formation was increased (statistically significant, $p < 0.05$) at doses ranging from 0.1 to 10 µg/mL.

Kruszewski et al. (2013) investigated the effects of AgNPs (20 or 200 nm in diameter) on DNA damage in human cell lines. After 2 hours incubation, 20 nm particles were agglomerated to 87–135 nm agglomerates. The 200 nm particles were agglomerated to 212–271 nm. The two sizes of particles were added to HEPG2, HT29 or A549 human cell lines in concentrations ranging from 10 to 100 µg/mL. DNA damage was measured with comet assay, oxidative base damage was recognised by formamido-pyrimidine glycosylase (FPG) and estimated by use of the FPG + comet assay and frequencies of histone H2AX foci and MN. No effects were observed on the frequency of histone

H2AX foci and induction of MN. Effects were observed in the comet assay both with and without FPG enzyme at concentrations of 10 µg/mL and above.

Karlsson et al. (2014) used a recently developed reporter assay based on mouse embryonic stem (mES) cells that uses GFP (green fluorescent protein)-tagged biomarkers (ToxTracker) for detection of DNA damage, oxidative stress and general cellular stress upon exposure to AgNPs (10 and 40 nm average size). In addition, the conventional alkaline comet assay (with and without FPG glycosylase for oxidative DNA lesions) was carried out. In the experimental condition of this study, AgNPs (5–50 µg/mL) were negative in comet assays and did not elicit neither DNA replication stress nor oxidative stress of p53-associated cellular stress.

Sahu et al. (2014) evaluated the genotoxicity of AgNPs in the human hepatoma HepG2 and human colon carcinoma Caco2 cells using the cytokinesis block-micronucleus assay with acridine orange staining and fluorescence microscopy. Cells were treated for 4 and 24 h with aliquots of a standard solution of citrate AgNPs (0.962 mg Ag/mL) at the final concentrations of 0.5–15 µg/mL. Average diameter of nanoparticles, determined by TEM, was 20.4 nm. A statistically significant increase in MN was observed in both cell types after 4 h exposure to 10 and 15 µg AgNPs/mL; after 24 h exposure significantly increased frequencies of cells with MN were observed at 0.5 µg/mL and above in HepG2 cells, and at the top dose of 15 µg/mL in Caco2 cells. In the range of doses applied, treatments did not elicit any significant cytotoxic/cytostatic effect, as measured by the cytokinesis-block proliferation index.

Vecchio et al. (2014) used a high-throughput screening platform based on the cytokinesis-block micronucleus assay, on-chip cell sorting, and automated image analysis to evaluate the cytotoxic and genotoxic effects of AgNPs of different size (10 and 70 nm) in primary human lymphocytes. Data show a significant genotoxic activity (induction of MN) with all AgNPs at the highest tested dose of 10 µg/mL, while the lower doses of 0.1 and 1 µg/mL were ineffective. AgNPs-induced genotoxicity was in part lymphocyte subtype dependent, with most pronounced response in CD2+ and CD4+ cells.

Butler et al. (2015) investigated how physico-chemical properties of AgNPs affect their cellular uptake and genotoxicity. To this aim, AgNPs of different size (10, 20, 50 and 100 nm) and silver nitrate (AgNO3) were tested for mutagenicity (Ames test), clastogenicity and primary DNA damage (in flow cytometry-based micronucleus test and comet assay in human monocyte and T cell lines). Cellular uptake concurrently evaluated by TEM. AgNPs of all tested sizes, as well as silver nitrate, were negative for mutagenicity in bacteria, which included strains sensitive to oxidative DNA damage (*E. coli* WP2 and *S.* Typhimurium TA102). No bacterial uptake of AgNPs could be identified by TEM. However, as AgNO3 either was not mutagenic in the Ames test, the lack of bacterial uptake of the AgNPs may not be the major reason for the lack of genotoxicity observed. On the other hand, in tests in mammalian cells, micronucleus and comet assay end points were inversely correlated with AgNPs size, with smaller NPs inducing a more distinct genotoxic response. The same genotoxic effects were also induced, with relatively higher efficiency, by silver nitrate. TEM results indicated that AgNPs were confined within intracellular vesicles of mammalian cells and did not penetrate the nucleus. These results suggest that silver ions may be the primary, and perhaps only, cause of genotoxicity elicited by AgNPs in mammalian cells.

3.2.3.2 *In vivo* studies

Additional studies, not evaluated by JECFA

Ionic silver

Eliopoulos and Mourelatos (1998) evaluated AgI for the ability to induce SCEs in P388 lymphocytic leukaemia cells cultured in the mouse peritoneal cavity at doses up to 100 mg AgI/kg bw. No induction of SCEs was observed. The Panel noted that this methodology, which recalls a host-

mediated assay, has not been validated nor further used to genotoxicity assessment, and considered the results of this study of limited or no relevance.

AgNPs

Kim et al (2008) tested AgNPs (average diameter 60 nm) within a 28-day oral toxicity study in rats. Sprague–Dawley rats (10/sex per group) were treated by gavage with daily doses of 30, 300 or 1,000 mg/kg AgNPs suspended in 0.5% carboxymethylcellulose. No increase in micronucleated polychromatic erythrocytes (PCEs), and no deviation of the poly/normochromatic erythrocyte ratio (PCE/NCE) was observed at sacrifice in treated rats compared to controls receiving the vehicle alone. According to the authors, the results suggested that the AgNPs did not induce genetic toxicity in male and female rat bone marrow *in vivo*. The Panel noted that no indication of exposure of bone marrow to the test material, as shown by the altered PCE/NCE ratio, is provided in this study. The Panel also noted that data on tissue distribution generated within the same study indicate a dose-dependent accumulation of silver in several tissues (kidney, liver, lungs, brain, stomach), whereas blood concentration of silver was only minimally elevated. Overall, the Panel concluded that the negative results obtained in this study are insufficient to rule out a genotoxic concern.

Ordzhonikidze et al. (2009) evaluated the toxic and genotoxic effects of AgNPs (size 9±6 nm) in BALB/c mice injected intraperitoneally (i.p.). The effect of the AgNPs was compared to those of the anionic surfactant (AOT), used as AgNPs stabiliser and silver nitrates. Acute toxicity of tested material decreases in the sequence AgNPs>AOT>>AgNO3. Genotoxic effects were assessed by the abnormal sperm heads test and neutral comet assay in splenocytes. The frequencies of abnormal sperm heads, evaluated 21 days after treatment, was similar in mice injected with AgNPs (1.6 mg ionic silver /L) and AOT (5mM), but higher (about 1.5-fold) than in control mice. At the same doses, corresponding to ½ LD50, comet assay showed an increase in the DNA percentage in the comet tail in spleen cells of mice injected with both AgNPs and AOT. However, the Panel noted that the sperm head abnormality test is not a genotoxicity end-point, as sperm morphology can also be affected by cytotoxicity. The Panel also noted a number of inconsistencies and shortcomings in the comet assay, performed with an inadequate (neutral) protocol, without a positive control and with inappropriate study design, averaging data from 14 mice sacrificed at seven different time points (two per point). Overall, the Panel concluded that this study cannot be considered for risk assessment.

Ghosh et al. (2012) investigated the genotoxicity of AgNPs in bone marrow cells of mice. AgNPs of 120 nm in diameter were administered intraperitoneally to Swiss albino male mice (8–12 weeks old, weight 25–30 g). There were six groups of five male mice each. The following groups were investigated: 1) negative control, 2) positive control (i.p. injection of mitomycin), 3) positive control (i.p. cyclophosphamide), groups 4) to 7) were single i.p. injection of AgNPs at 10, 20, 40 and 80 mg/kg bw, respectively. The animals were euthanised after 18 h of exposure. Then the chromosome aberration test and the comet assay were performed. Results were as follows: A statistically significant increase in chromosomal aberrations (mainly chromatid breaks) in bone marrow cells were found with all doses of AgNPs ($p < 0.05$). DNA damage, as measured by the comet assay, was statistically significantly ($p < 0.05$) increased but only in the two lowest doses of 10 and 20 mg AgNP/kg bw groups and not in the 40 and 80 mg AgNP/kg bw groups. ROS generation in bone marrow was also quantified by flow cytometry: according to the authors the results obtained indicate significant ROS generation following treatment with 10 and 20 mg AgNP/kg bw, whereas ROS generation at the subsequent concentrations was negligible and comparable to control (data not shown). The Panel noted that as described the particles appeared to be out the size range defined as nanoparticles in the EFSA Guidance (EFSA, 2011), and furthermore the route of exposure used in this study may have limited relevance for the assessment of the *in vivo* genotoxic hazard *in vivo* associated with oral intake of AgNPs.

Gromadzka-Ostrowska et al. (2012) injected male Wistar rats, 24 animals/group, (age 14 weeks, body weight 308.1 $\pm$ 22.4 g) via the tail vein with a single dose (5 mg/kg bw or 10 mg/kg bw) of 20 nm AgNPs (Groups AG I and AG II) or with 5 mg/kg bw of 200 nm silver particles (group Ag III). A

control group was injected with 0.9% NaCl solution. Animals were sacrificed 24 h, 7 days and 28 days after injection. Epididymal sperm count, sperm morphology, sperm cell DNA damage (using the comet assay) and histopathological examination of the testis were performed. No differences in body weight, food and water consumption were observed. Epididymis weight and testis weight were comparable among the groups. Epididymal sperm count was decreased in the AG I group after 24 h and 28 days when compare to the control. The frequency of abnormal sperm was comparable in the treated and the control groups. The comet assay showed that DNA damage (% DNA in the tail in the germ cells was increased at 24 hours in the AG I and Ag II groups, then decreased after 7 and 28 days. No difference was found for the AG III group. Histopathological examination showed effects (differences of the seminiferous tubule morphology, wider intercellular spaces and higher vacuolisation of the germinal epithelium) in the testis of the animals of the AG III group. The Panel noted that the application of the comet assay to germ cells is complicated by a number of technical and theoretical considerations, and that its use for regulatory purposes has been not recommended (MacGregor, 2015).

Dobrzynska et al. (2014) injected intravenously male Wistar rats (7 per group) with 5 or 10 mg/kg bw spherical AgNPs (average diameter 20 nm) or 5 mg/kg bw Ag spherical microparticles (average diameter 200 nm). Animals were sacrificed 24 hrs, 1 week and 4 weeks later, and genotoxicity evaluated in bone marrow cells by comet and micronucleus assays. No genotoxicity was detected in bone marrow cells by comet assays at any sampling time. A significant (two/three-fold) increase in micronucleated polychromatic erythrocytes (PCE), stained with the conventional May-Gruenwald and Giemsa stains, was reported in all treated groups sacrificed 24 h and 1 week after treatment, and also after 4 weeks for the high-dose nanoparticles group. In the same treated animals, no increase in the number of MN in bone marrow reticulocytes stained with acridine orange was observed. The Panel noted that polychromatic erythrocytes and reticulocytes represent the same cell type, i.e. immature erythrocytes detected with different staining procedures, and thus, there is no reason for the divergent results reported. Moreover the Panel noted that the approach followed up for the statistical analysis of results was incorrect, considering cells rather than animals as statistical units, while data show a large inter-animal variability (CV of 1.7 among solvent controls). This raises doubts on the biological significance of the positive result reported. Overall, the Panel concluded that the results of this study should not be considered for risk assessment.

El Mahdy et al. (2014) injected i.p. mature female albino rats (5 per groups) with 1, 2 and 4 mg/kg bw AgNPs (8.7 nm) daily for 28 days. At the end of treatment chromosomal aberrations were scored in 50 bone marrow cells per animal. A statistically significant increase in structural chromosomal aberrations was reported in treated animals compared to controls receiving the vehicle (distilled water) alone. The Panel noted that 'centromeric attenuations' were the most frequent alteration observed and included in the computations of structural chromosomal aberration, whereas 'centromeric attenuation' consists in a discolouration of the centromeric region with unknown biological significance. The only other aberrations recorded were chromatid deletions which increased in treated animals with no clear relation with dose (1, 3, 7 and 4 deletions in control, low, middle and high dose, respectively). The Panel also noted that such findings were provided by the scoring of just 50 cells per animal, whereas OECD Guideline 475 recommends to score at least 200 metaphases per animal. Based on these concerns, the Panel considered the results of this study as inconclusive.

Patlolla et al. (2015) evaluated the hepatotoxic and genotoxic effects elicited by oral administration of AgNPs to rats. AgNPs (10 nm diameter), suspended in deionised water, were given by gavage to groups of five adult male Sprague–Dawley rats at 5, 25, 50 or 100 mg/kg bw once a day for 5 days. Animals were sacrificed 24 h after last treatment, blood collected and liver excised for the analysis of the following biomarkers: i) liver function enzymes (ALT/glutamic-pyruvate transaminase (GPT), AST/glutamic oxaloacetic transaminase (GOT), ALP) in serum; ii) reactive oxygen species (ROS) and lipid hydroperoxide (LHP) in liver homogenate; iii) DNA damage in liver by alkaline comet assay; iv) liver histopathology. The results obtained show a dose-related increase in serum markers of altered liver function, as well as ROS and LHP generation in liver homogenate. The increases reached

statistical significance at the two highest dose levels (50 and 100 mg/kg bw per day). Histopathological examination of liver tissue highlighted a dose-related increase in frequency and severity of morphological alterations, which were severe at the highest dose displaying central vein damage, hepatocellular vacuolisation, necrosis and pycknosis. A dose-related increase in percentage tail DNA, which attained statistical significance at 50 and 100 mg/kg bw per day, and was also observed in comet assays with liver homogenates. The authors concluded that oral administration of high doses of AgNPs caused oxidative stress, DNA damage and hepatotoxicity in rats. The Panel agreed with this conclusion. However, concerning genotoxicity, the Panel noted that no concurrent evaluation of cell survival was performed in comet assay, and that heavily damaged cells indicative of cell toxicity, the so-called hedgehogs, were not recorded separately as recommended. Therefore, according to the OECD TG 489 recommendation, the Panel concluded that the positive results reported in this study in association with overt organ toxicity should be evaluated with caution for genotoxic risk assessment. The Panel also noted that, according to the results reported, an extensive release of Ag ions (35–70%) occurred when AgNPs were disperse in deionised water, and thus considered that ionic silver may have contributed to the adverse effects reported in this study.

Summary

The limited information available, indicate that ionic silver is non-mutagenic in bacteria but genotoxic and clastogenic in mammalian cells *in vitro* (Butler et al., 2015). No information is available on the genotoxic potential of ionic silver *in vivo*.

Concerning AgNPs, negative results were obtained in mutation tests in bacteria (Li et al., 2012; Kim et al., 2013; Butler et al., 2015), but positive results have been reported in the majority of *in vitro* studies performed in mammalian cells. In these studies, AgNPs induced MN in human (Li et al., 2012; Vecchio et al., 2014; Sahu et al., 2014; Butler et al., 2015) and rodent cells (Kawata, 2009; Li et al., 2013; Kim et al., 2013), DNA lesions detectable by comet assays, optimised for the detection of oxidative damage, in a variety of human (Kawata et al., 2009; Hackenberg et al., 2011; Asare et al., 2012; Flower et al., 2012; Kruszewski et al., 2013; Butler et al., 2015) and rodent (Ahamed et al., 2008; Kim et al., 2010; 2013; Mei et al., 2012) cell lines and gene mutations in mouse lymphoma cells (Mei et al., 2012). Data suggest that the release of silver ions from nanoparticles can contribute or even entirely account for the *in vitro* genotoxicity of AgNPs (Kawata et al., 2009; Butler et al., 2015).

Fewer studies have investigated the *in vivo* genotoxic potential of AgNPs. No induction of MN was observed in rat bone marrow after oral exposure of 30 to 1,000 mg/kg bw for 28 days, with no proof of bone marrow exposure (Kim et al., 2008) whereas oxidative stress and DNA damage was observed in another oral study in rats (Patlolla et al., 2015), but the Panel considered these findings not conclusive. Chromosomal aberrations were induced in bone marrow cells of mice after intraperitoneal exposure (Ghosh et al., 2012), but the Panel noted that the i.p. route of administration is not relevant for the evaluation of risk from oral exposure. Other *in vivo* studies provided inconclusive or unreliable results.

In conclusion, there are no data available to evaluate the *in vivo* genotoxicity of ionic silver. Concerning AgNPs, the available studies provide clear evidence of a genotoxic potential in various *in vitro* test systems. The *in vivo* oral genotoxicity studies performed provide less conclusive evidence, and do not allow a definitive assessment of the possible genotoxic hazard associated with oral exposure to AgNPs.

Overall, the Panel concluded that the available data are inadequate to evaluate the genotoxic hazard associated with the use of silver as food additive.

3.2.4. Chronic toxicity and carcinogenicity

No data were submitted to EFSA following a public call for data. The two studies evaluated by JECFA (JECFA, 1977) investigated the occurrence of tumours following implantation of foil, platelets and pellets of silver or dental alloy under the skin of mice and rats; these studies are not considered of relevance for the evaluation of silver as a food additive. The studies identified in the literature search are summarised below.

Additional studies, not evaluated by JECFA

Ionic silver

Olcott (1948) has studied the effects of orally administered silver nitrate and silver chloride in rats (number and sex not further specified). Various concentrations of the silver salts were assessed. When rats were given a concentration of 1% of the silver salts in the drinking water, they did not survive (equivalent to 317 and 375 mg ionic silver/kg bw/day for silver nitrate and silver chloride, respectively[25]). With a concentration of 0.4% of the silver salts in the drinking water two rats were kept alive for 500 days (equivalent to 127 and 150 mg ionic silver/kg bw/day for silver nitrate and silver chloride, respectively[25]). When given a 1:1000 dilution of the silver salts in about 1:300 sodium thiosulphate for their lifetime (equivalent to 32 and 38 mg ionic silver/kg bw/day for silver nitrate and silver chloride, respectively[25]) the life span of the rats was not shortened. A range of organs was investigated; left heart ventricle hypertrophy was the only finding reported. The study could not be used for risk assessment as the reporting was limited.

Forty weanling male Wistar rats (age and body weight not specified further) were administered a 0.25 % silver nitrate solution via the drinking water for up to 8.5 months (equivalent to 79 mg ionic silver/kg bw/day[25]). After 10 weeks, two rats were euthanised and the eyes were processed for electron microscopy. The remaining rats were divided into two groups: 1) A group that continued with the same solution for the next 6 months and 2) a group that was shifted to water for 6 months. A slightly lower rate of body weight gain was reported until about 23 weeks after the start and at this point some animals began to loose weight and eventually died. The group of rats that had withdrawal of silver nitrate regained their body weight (Matuk et al., 1981).

Overall, no studies on the carcinogenic potential of either ionic silver compounds or AgNPs have been identified. In rats, retarded growth and stained muzzles were the only effects reported following long-term exposure to ionic silver (up to 8.5 months approximately 81 mg ionic silver/kg bw/day, (Matuk et al., 1981) and 60 weeks, approximately 118 mg ionic silver/kg bw/day (Walker 1971)).

3.2.5. Reproductive and developmental toxicity

No data were submitted to EFSA following a public call for data. No studies were evaluated by JECFA (JECFA, 1977). Additional studies identified in the literature search are summarised below.

Additional studies, not evaluated by JECFA

Ionic silver

Reproductive toxicity

The toxicity of silver acetate (purity 99%) was studied in Sprague–Dawley rats (n=20/sex per group) when administered in drinking water in an one-generation reproduction and fertility test (Documentation provided to EFSA No5). Silver acetate was given in the drinking water at dose levels resulting in administration of 0, 0.4, 4 or 40 mg silver acetate/kg bw/day (0, 0.26, 2.6 or 26 mg ionic silver/kg bw/day). Parental male animals were exposed 10 weeks prior to mating and parental female

[25] Calculated by the Panel according to EFSA Scientific Committee (2012).

animals for 2 weeks prior to mating. The F1-pups were sacrificed on postnatal day (PND) 26. Special attention was given to the thymic development.

No clinical signs, changes in body weight and food intake were observed during the study. However, a reduction was observed in fluid consumption of the male and female rats of the high-dose group during the premating period. The author considered this as a consequence of taste aversion. Fluid consumption was also decreased in the high-dose group during gestation and in all silver acetate groups during lactation.

The fertility was decreased in the high-dose group compared to the control and the low- and mid-dose group. The number of pups born alive was decreased in the high-dose group. Reduced pup survival observed in the mid-dose group compared to the control group was not observed in the other dose groups. Data suggested that in the high-dose group pups loss occurred during gestation and early lactation and in the mid-dose group at a later time point. Pup loss (PND 4–21) was decreased in the high-dose group compared to the control, low- and mid-dose groups.

Pup weights of the mid-dose group were decreased on PND 0, 4, 7 and 21 (on PND 21 not statistically significantly) and the number of runts in this group was increased on PND 4, 7 and 21. The author stated that it appeared that the F1-pups from the high-dose group that were sensitive to silver acetate exposure died early but that those that survived recovered by PND 21. Furthermore, they stated that data suggest that the growth rate in F1-female pups of this group that were sensitive to silver acetate did not return to control values by PND 26.

At necropsy of the parental animals and F1 pups on PND 26, no treatment-related effects were observed on organ weight (relative to brain weight) of the thymus, spleen, heart, kidney, liver, ovaries, testes, epididymides, apart from the decreased stomach weight in the parental females and the male and female F1 pups of the high-dose group and the kidney weight of the F1 pups of the mid-dose group.

The only effect found in the clinical chemistry of the parental animals was an elevated serum glucose level in the high-dose group. No adverse effects were observed in the female F1 pups.

In male F1 pups, the following effects were observed on clinical chemistry: a decrease in blood urea nitrogen (BUN) in the all silver acetate treated groups; increase in serum glucose in the high-dose group; increase in serum calcium in the low- and mid-dose group but not in the high-dose group and a decrease in the BUN/creatinine ratio in the mid- and high-dose group.

Exposure to silver in drinking water caused deposition in a number of tissues of the parental (F0) animals but did not cause any significant histopathological changes. No gross effects or histopathological changes were observed in the F1 pups (exposed *in utero* and during lactation) on PND 26.

Based on the presence of runts, pup death and delayed pup growth the authors considered that 0.4 mg silver acetate/kg bw/day (0.26 mg ionic silver/kg bw/day) was the NOAEL for this study. The Panel agreed with this conclusion.

Developmental toxicity

Rats

Shavlovski et al. (1995) investigated the role of ceruloplasmin in the transport of copper when embryotoxicity of silver chloride was induced in rats. Inbred albino female rats (body weight 180–200 g, age and strain not specified further) were given 50 mg silver chloride/animal per day in the feed (with a body weight of 200 g this corresponds to 250 mg silver chloride/kg bw/day corresponding to 188 mg ionic silver/kg bw/day). The rats were exposed from gestation day (GD) 7–15 (five pregnant animals/group) or GD 1–20 (20 pregnant animals/group). On GD 20, animals were euthanised. The

number of live and dead fetuses, as well as malformations was recorded and corpora lutea were counted. Fetuses were weighed and the conditions of their organs were assessed. A range of biochemical parameters were measured in the tissues. For dams exposed from GD 1–20, the postimplantation loss was 36% ($p < 0.001$), fetal weight was decreased ($p < 0.001$) and the number of fetuses having visceral aberrations was considerably higher than in the control group. In addition, the new-born animals all died within the first 24 h after birth. The Panel noted that Shalovski designed this study to investigate the role of ceruloplasmin but standard parameters (body weight, feed consumption) and dose-response assessments were not included. Only one high dose was tested for which no maternal effects were observed after exposure from GD 6 to 15 and exposure from GD 1 to 20. However, it may be assumed that the absence of any detectable copper carrying, enzymatic active ceruloplasmin in the blood and an absence of detectable copper in the serum in the dams and in the fetuses and placenta is the cause of the observed developmental effects.

Silver acetate was administered daily to mated Sprague–Dawley rats (25 animals/group) by gavage from GD 6 to 19 at doses of 0, 10, 30 or 100 mg/kg per day (vehicle 1% aqueous methylcellulose) (NTP, 2002). Silver administration was equivalent to 6.5, 19.4 or 65 mg ionic silver/kg bw/day. Females were sacrificed on GD 20 followed by a full fetal pathological examination. One animal was removed from the high-dose group due to a misdosing and one confirmed pregnant female in the high-dose group was euthanised on GD12 due to morbidity. Treatment-related clinical signs were noted primarily in the mid- and high-dose groups and consisted of weight loss, rooting after dosing and piloerection. A significant ($p < 0.05$) decreasing linear trend was noted for maternal body weight on GD 12, but there were no statistically significant differences between the control group and any treated group. Feed and water consumption did not exhibit dose-related differences between the control group and silver acetate-treated group. There were no differences in the number of corpora lutea and number of implantations. Postimplantation loss, number of live and dead fetuses, and the sex ratio did not differ among groups. An increasing trend was observed for the percent litters with late fetal deaths. Average fetal body weight/litter (sexes combined) and average male fetal body weight/litter exhibited a significant decreasing trend, but no significant pairwise differences between treated groups and the control group. No statistically significant effects were noted for average female body weight. No toxicologically relevant differences were observed in the incidences of fetal malformations or variations. The authors noted that the maternal NOAEL was 10 mg silver acetate/kg bw/day (equivalent to 6.5 mg ionic silver/kg bw/day) based on the clinical signs including weight loss and considered the NOAEL for developmental toxicity to be 100 mg silver acetate (equivalent to 65 mg ionic silver/kg bw/day). The Panel agreed with this conclusion.

Summary

Overall, in an oral one-generation reproductive toxicity study with silver acetate in drinking water at dose levels of 0, 0.4, 4 or 40 mg silver acetate/kg bw/day (0, 0.26, 2.6 or 26 mg ionic silver/kg bw/day) in rats, a NOAEL for developmental effects (increased number of pups, pup death and decreased weight gain of pups) of 0.4 mg silver acetate/kg bw/day (0.26 mg ionic silver/kg bw/day) was observed (Documentation provided to EFSA No5). The NOAEL for fertility was 4 mg silver acetate/kg bw/day (2.6 mg ionic silver/kg bw/day).

In a prenatal developmental toxicity study, developmental toxicity of ionic silver was observed when rats were dosed with silver chloride (188 mg ionic silver/kg bw/day) on GD 1–20 (Shavlovski et al., 1995). No developmental effect was observed by the same authors when rats were only dosed with silver chloride from GD 7–15. This study was only conducted at one-dose level in a low number of animals and maternal toxicity was not described properly. The effects on ceruloplasmin after longer administration were emphasised by the authors. The Panel noted that the study was performed with a high dose.

In another prenatal developmental study (NTP, 2002) with silver acetate performed according the current guidelines at dose levels of up to 100 mg/kg bw/day (65 mg ionic silver/kg bw/day)

administered from GD 6–19, a NAOEL for developmental toxicity was observed at 65 mg ionic silver/kg bw/day as the NOAEL for maternal toxicity was 6.5 mg ionic silver/kg bw/day.

The Panel noted that silver ions affected developmental toxicity at a much lower level (NOAEL 0.26 mg ionic silver/kg bw/day) in the one-generation reproductive toxicity study.

3.2.6. Hypersensitivity, allergenicity, intolerance

3.2.6.1 Allergy

The Panel noted that reports of people suffering from silver allergy after exposure to silver (mostly in jewels or dental amalgams) are usually confounded by the simultaneous presence of nickel, a known sensitising metal. These observations are not relevant to the safety assessment of silver as a food additive.

3.2.6.2 Immunotoxicity

Several recent studies *in vitro* and *in vivo* in mice and rats, have reported that administration of AgNPs induces various immunotoxic effects (Lappas, 2015).

In mice treated orally Park et al. (2010) (study design described in Section 3.2.2.1) for 14 days with AgNPs (22 nm, 42 nm and 71 nm; suspended in 0.5% carboxy methyl cellulose), several alterations in immunological parameters were reported. Cytokines including IL-1, IL-6, IL-4, IL-10, IL-12 and TGF-α were increased in a dose-dependent manner by repeated oral administration. In addition, B cell distribution in lymphocyte and IgE production were increased. Based on these results, the authors suggested that repeated oral administration of AgNPs may cause organ toxicity and inflammatory responses in mice.

Van der Zande et al. (2012) investigated the immunotoxicity of AgNPs and silver ions in rats. Male Sprague–Dawley rats (5/group, 6 weeks old, start body weight about 245 g) were exposed daily by oral gavage for 28 days to 90 mg/kg bw of AgNPs (18 nm, non-coated or 12 nm, PVP-coated, in diameter) or 9 mg/kg bw of silver nitrate (corresponding to 6 mg ionic silver/kg bw). Included were also wash-out groups identically exposed to silver but not euthanised until day 36 or day 84. Immunotoxicity was evaluated by testing the proliferation of T- and B-cells isolated from spleen and mesenteric lymph nodes in response to lipopolysaccharides (LPS) or Concanavalin A. Cytokine levels in culture media from these proliferating T- and B-cells, and the activity of natural killer (NK)-cells isolated from the spleen were also measured. Finally, antibody levels in blood were evaluated. No immunotoxicity was detected.

After oral exposure in drinking water of rats to silver acetate (Ag-Ac) 0, 0.4, 4 and 40 mg/kg bw/day (0, 0.26, 2.6 or 26 mg ionic silver/kg bw/day) as described in Section 3.2.5 (Documentation provided to EFSA No5), splenic and thymic lymphocyte subsets from postnatal (PN) 4- and 26-day-old pups were assessed by flow cytometry for changes in phenotypic markers. Functional indices included natural killer (NK) activity and mitogen-induced lymphocyte proliferation. Spleens from PN 4-day pups had lower percentages of CD8+ lymphocytes in 4 and 40 Ag-Ac groups and reduced Concanavalin A response in all three Ag-Ac groups. Changes in phenotypic markers in splenocytes from PN 26-day pups included significantly lower TCR+ cells in rats fed 4 and 40 mg Ag-Ac and higher B cell population in those that were fed 40 mg Ag-Ac. In conclusion, maternal exposure to Ag-Ac had a significant impact on rat splenic development especially in the early lactation period, but there was no impact on thymic development. The Panel noted that the immunotoxic effects reported mostly pointed to an effect of silver on the phenotype and maturation of the developmental splenic T cell population. The Panel also noted that at the lowest dose administered of 0.4 mg silver acetate, a reduced Concanavalin A response was observed. This dose corresponds to a lowest-observed-adverse-effect level (LOAEL) of 0.26 mg ionic silver/kg bw/day.

Małaczewska (2014) reported that 28-day oral administration to mice of different doses (0.25, 2.5, 25 mg/kg diet equivalent to 0.05, 0.5 and 5 mg/kg bw/day[26]) of silver nanocolloid (10–20 nm) decreased the counts of monocytes in the animals' blood and induced an increase in CD4+/CD8+ T cell distribution, a decrease in NK and NKT cell distribution (doses of 0.5 and 5 mg/kg bw/day) and an increased CD4+:CD8+ ratio (5 mg/kg bw/day). Silver nanocolloid also affected the activity of cells, depressing the proliferation of lymphocytes at the lowest dose tested (0.05 mg/kg bw/day diet) and stimulating phagocytosis as well as the respiratory burst of granulocytes and monocytes (all doses).

Hamilton et al. (2014) studied the sensitivity of a variety of macrophage and epithelial cell lines to 20 nm and 110 nm AgNPs. They reported that 20 nm nanoparticles were more toxic to macrophages and epithelial cells than were 110 nm nanoparticles. According to the authors, this could be due to the more rapid dissolution of the smaller particles in acidic phagolysosomes, which is consistent with silver ion mediated toxicity.

Haase et al. (2014) has reported that the effects of AgNPs and ionic silver on neutrophils and macrophages were similar; both triggered the release of neutrophil extracellular traps and inhibited the formation of nitric monoxide and protein phosphatase activity, and induced increased intracellular levels of ROS.

The Panel noted that the outcomes of all these studies were inconsistent. This could be due to different material, doses, duration of exposure, and animal models used but overall the Panel considered that ionic silver and AgNPs may have an effect on the immune system.

3.2.7. Other studies

3.2.7.1 Animals

Ionic silver

In rats (6/group) given drinking water containing 0.5, 2 or 20 mg Ag/L (No further details regarding the silver compound, except that the description in the JECFA evaluation indicate that silver was administered as a soluble salt, i.e. ionic silver) for 6–12 months, the nucleic acid level in brain and liver was decreased after 1 year at 2 mg Ag/L. At 20 mg Ag/L, the RNA and DNA contents of the brain were increased after 6 months and dystrophic changes in the brain accompanied by a decrease in nucleic acid level were observed after 12 months. The liver was less sensitive towards silver than the brain (Kharchenko et al., 1973, cited in JECFA, 1977).

In rabbits (8/group) administered 0, 0.00025, 0.0023, 0.025 or 0.25 mg Ag/kg (No further details regarding the silver compound; the unit is probably mg Ag/kg bw) via their drinking water for 11 months *marked effects on immunological capacity (measured as phagocytosis)* and histopathological changes of nervous, vascular and glial tissue of the encephalon and medulla were observed at the two highest dose levels (0.025 and 0.25 mg Ag/kg bw). No effects on the haemoglobin concentration, red blood cell count, differential white blood cell count, *proteinogenic function of the liver* and serum sulfhydryl (SH) were noted. *Rats treated with same amounts of silver showed affected conditioned reflexes* (Barkov and El piner, 1968, cited in JECFA, 1977).

Rungby and Danscher (1984) investigated the potential effect of silver on behaviour of animals. Female NMRI mice (20 animals, 60 days old at the beginning of the experiment, body weight not reported) had their drinking water replaced by a 0.015% silver nitrate solution for 125 days (equivalent to 14 mg ionic silver/kg bw/day[26]). Thereafter, the mice were given normal drinking water again. Twenty non-exposed females served as controls. Ten days after termination of silver administration, the mice were tested with regard to activity levels. The silver exposed mice were found to be hypoactive as measured by open field behaviour in the cage.

[26] Calculated by the Panel according to EFSA Scientific Committee (2012).

Ionic silver/ AgNPs

Mice

AgNPs (3–20 nm, not further specified) were dosed to Swiss albino mice by gavage at doses of 0, 5, 10, 15 and 20 mg/kg bw/day for 21 days (Shahare and Yashpal, 2013). Body weight was decreased in all dose groups. The weight loss was the highest in the 10 mg/kg bw group. The authors further only described in this dose group. Damaged intestinal epithelium was found in mice at 10 mg/kg bw/day for 21 days. The authors assumed that loss of microvilli reduced absorptive capacity of the intestinal epithelium and hence weight loss.

Rats

Hadrup et al. (2012 a,c) investigated the toxic and neurotoxic potential of AgNPs and ionic silver in rats. Female Wistar rats (4 weeks old) were administered vehicle control, silver acetate (9 mg ionic ionic silver/kg bw/day), or AgNPs (14 nm in diameter; PVP-coated) at 2.25, 4.5 or 9 mg/kg bw/day by oral gavage for 28 days; males were only given the vehicle control and 9 mg AgNP/kg bw/day for 28 days. Body weight, macroscopic and microscopic pathology and a range of biochemical and haematological parameters, as well as brain neurotransmitters were measured. Perturbation in brain dopamine ($p < 0.01$ and 0.001), noradrenaline ($p < 0.05$) and serotonine ($p < 0.01$) were observed following both ionic silver and AgNPs. In addition ionic silver led to decreased body weight gain ($p < 0.01$), decreased relative thymus weight ($p<0.05$) and increased plasma ALP ($p < 0.05$) and decreased plasma urea ($p < 0.05$). AgNPs at 9 mg/kg bw/day increased the haematocrit. Both ionic and AgNPs increased urine uric acid (only statistically significantly for AgNPs $p < 0.001$) and allantoin urine concentration ($p < 0.01$ and 0.001). In an accompanying *in vitro* investigation, AgNPs, ionic silver (silver acetate) and a 12 kDa filtered subnano silver particle fraction were used to investigate cell death mechanisms in neuronal-like cells; the effect of subnano silver in the silver nanoparticle preparations strongly suggested that the toxic effects of AgNPs were mediated by free ions as toxic effects *in vitro* on viability (including apoptosis) could be explained by the subnano fraction and ionic silver.

Van der Zande et al. (2012) investigated the hepatotoxicity of AgNPs and silver ions in rats. Male Sprague–Dawley rats (5/group, 6 weeks old, start body weight about 245 g) were exposed daily by oral gavage for 28 days to 90 mg/kg bw of AgNPs (18 nm, non-coated or 12 nm, PVP-coated, in diameter) or 9 mg/kg bw of silver nitrate (corresponding to 6 mg ionic silver/kg bw). Included were also wash-out groups identically exposed to silver but not euthanised until day 36 or day 84. Hepatotoxicity was evaluated by analysis of alanine aminotransferase and aspartate aminotransferase levels in plasma. No hepatotoxicity was detected.

Williams et al (2015) described studies on the GI tract of male and female Sprague–Dawley rats using ileal samples from a good laboratory practice (GLP)-compliant NTP study (details of which (biodistribution, bioaccumulation and histopathological examinations) are due to be reported separately and were not available to the Panel). Three sizes of citrate-stabilised AgNPs (10, 75 and 110 nm) and silver acetate were used. The Panel noted that a full interpretation of the published findings cannot be made in the absence of the data on biodistribution, bioaccumulation and histopathological examinations which are not included in the paper but will be published elsewhere. The Panel also noted that the reported effects were only determined in one part of the small intestine (ileum) and may not be representative of the whole GI tract such as the jejunum or colon where there are different microbial populations. Furthermore reported details of the bacterial isolate preparation methods are limited and it was not possible to ascertain whether this occurred under aerobic or anaerobic conditions and the effectiveness of these conditions.

Effect of silver on copper metabolism.

In the study by Ilyechova et al. (2014), two groups of animals received 50 mg silver chloride/kg bw/day: one group of adult rats received the silver-diet for 1 month (Ag-A1) and another group received the silver-diet for 6 months from birth (Ag-N6). The animals in the Ag-N6 group were first fed by females, which received the Ag-diet from the first day of lactation. In Ag-A1 rats, a dramatic decrease in copper status indexes manifested as ceruloplasmin-associated copper deficiency. In Ag-N6 rats, copper status indexes decreased only twofold as compared to control rats. In rats of both groups, silver entered the bloodstream and accumulated in the liver. Silver was incorporated into ceruloplasmin (Cp). In the liver, a prolonged Ag-diet caused a decrease in the expression level of genes associated with copper metabolism.

3.2.7.2 Humans

The Panel was aware that there are numerous data reporting adverse effects of silver due to its use in the medical field (Lansdown, 2010; Maillard, 2013) or as a result of occupational exposure (Drake and Hazelwood, 2005). If these observations confirm that prolonged exposure to very high doses of elemental silver can be responsible for the development of toxic effects, these are mostly due to the release of biologically active silver ions, and they are consecutive to exposure, which is very high and/or not comparable to the exposure resulting from the use of silver as a food additive. Therefore, these data were not directly considered in the risk assessment of silver as a food additive but they reported some useful information about the possible human effects resulting from silver toxicity.

The data indicated that the main reported effect after exposure to high doses of elemental silver in an occupational setting was argyria, which was not associated with pathological damage in a specific target organ. On the contrary, exposure to soluble silver compounds present in drugs may produce toxic effects, including liver and kidney damage, irritation of the eyes, skin, respiratory and intestinal tract, and changes in blood cells. No carcinogenic effects were reported and silver allergy was extremely rare.

Overall, the Panel noted that in the case of medical and occupational exposure to silver, the doses and/or the route of exposure (inhalation, no inclusion in a food matrix) were usually irrelevant to the exposure resulting from the use of silver as a food additive. The Panel also noted that the health risks associated with systemic absorption of ionic silver were low. Argyria and argyrosis are the principle observable changes associated with long-term exposure to ingestion or inhalation of high doses of metallic silver or ionisable silver compounds. The Panel noted that, in these contexts, the possible effects resulting from oral exposure to AgNPs were poorly documented.

4. Discussion

Following a request from the EC, the ANS Panel was asked to deliver a scientific opinion re-evaluating the safety of silver (E 174) when used as a food additive. The Panel based its evaluation on previous evaluations and on the additional literature that became available since then and the data available following a public call for data. The Panel noted that not all original studies on which previous evaluations were based were available.

To assist in identifying any emerging issue or any relevant information for the risk assessment, EFSA has outsourced a contract to deliver an updated literature review on toxicological endpoints, dietary exposure, and occurrence levels of silver (E 174) which covered the period up to the end of 2014. Further update has been performed by the Panel.

Silver (E 174) is a food colouring authorised as a food additive in the EU that was previously evaluated by the SCF in 1975 (SCF, 1975) and by JECFA in 1977 (JECFA, 1977, 1978) and. None of the committees established an ADI. The previous evaluation by JECFA has been summarised and new available literature has been evaluated and incorporated. EFSA have also evaluated a number of silver

complexes intended for use in food contact materials latest in 2011 (EFSA, 2011) and classified silver in the SCF list 3 with a group of specific migration limit of 0.05 mg/kg food.

The Panel noted that the manufacturing process of powdered or particulate food additives resulted in material with a range of sizes. Although the mean or median size of the particles is generally significantly greater than 100 nm, a fraction can be present with at least one dimension below 100 nm. The material used for toxicological testing would have contained this nanofraction. The test requirements stipulated in current EFSA guidance documents and EC guidelines for the intended use in the food/feed area apply in principle to unintended nanoforms as well as to ENM. Therefore, the Panel considered that in principle for a specific food additive containing a fraction of particles with at least one dimension below 100 nm, adequately conducted toxicity tests should be able to detect hazards associated with this food additive including its nanoparticulate fraction. The Panel considered that for the re-evaluation of food additives this procedure would be sufficient for evaluating constituent nanoform fraction in accordance with the recommendation of the EFSA Nano Network in 2014 (EFSA, 2015).

Silver in food additive E174 is present in its elemental form. Specifications for silver have been defined in the EU in Commission Regulation (EU) No 231/2012. The purity is specified to be not less than 99.5% for silver-coloured powder or tiny sheets. Silver can also occur in crystalline form as a white metal.

The Panel noted that silver is used in foods as powder, crumbs or flakes of different sizes above 1 mm, but limited information has been provided by industry on distribution of particle sizes in powdered silver. However, there is some evidence that AgNPs could be released from the current application forms, as it has been observed by the data provided after the analysis of the AgNPs released from the coating of silver-coloured pearls for decoration of pastry, being reported an amount of 4.4×10^9 Ag nanoparticles/g of pearl. The mass concentration of the detected particles was 1.8 ± 0.6 µg/g pearl, representing the 20% of the mean concentration of silver in the pearls.

The Panel noted that in Commission Regulation (EU) No 231/2012, no information is included regarding the particle size of silver powder and therefore the characterisation of the particle size in the powder of E 174 should be included among the specifications. The fully characterisation should include the particles size distribution together with determination and quantification of any nanoparticulate material.

The Panel noted that AgNPs are released from confectionary pearls (Verleysen et al., 2015) and nanosilver is unstable and releases ions (see Section 2.5). The Panel was aware of the extensive database on ionic silver or AgNPs, however the relevance of these data to the evaluation of silver as a food additive (E 174) was not apparent. Therefore, the Panel considered these data could not be directly applied to the evaluation of the food additive.

Following oral exposure of animals to ionic silver or AgNPs, silver is systemically available. Silver concentrations in the organs were highly correlated to the size of the nanoparticles concentrations being higher in animals exposed to smaller nanoparticles and to the amount of silver ions released from the AgNPs. Bioavailability seems to be in the range of 2–20% depending on many factors including the animal species.

However, the Panel noted that, due to the many variables involved, the conversion rate of metal silver from nanoparticles to silver ions in biological systems is unknown. Moreover, the formation of ROS from the fraction of AgNPs which may be present in the food additive has not been determined. The rate of both processes depends on the size of particles and their relative surface.

Silver distribution has been reported to all organs and tissues of animals. Silver distribution to the brain following oral exposure has been described in several studies, which is in contrast to the conclusions of previous studies with silver nitrate or lactate, that silver would not cross the blood–

brain barrier (van Breemen and Clemente,1955;). However, it is also in the recent studies not clear whether silver is present in the brain endothelial cells or in the brain tissue. Silver ions were also detected in the milk of rat dams receiving a daily oral administration of silver chloride and in the liver and the brain of the pups. In rodents, silver is primarily excreted via the bile and faeces, but a small amount is also excreted via the urine.

The Panel noted that only one study described the fate of microsized silver particles in animals (Park et al., 2010). In this study, no silver was detected in any of the tissues of mice given an oral administration of microsized silver particles (323 nm), whereas silver was present in tissues of mice receiving a similar administration of nanosized silver particles (21 to 71 nm).

The Panel was aware that there are many data reporting distribution of silver in various human organs following prolonged exposure to very high doses of silver in different forms. The Panel was also aware that there are numerous data reporting adverse effects of silver due to its use in the medical field (Lansdown, 2010; Maillard, 2013) or as a result of occupational exposure (Drake and Hazelwood, 2005). Overall, the Panel noted that in the case of medical and occupational exposure to silver, the doses and/or the route of exposure (inhalation, no inclusion in a food matrix) were usually irrelevant to the exposure resulting from the use of silver as a food additive. The Panel also noted that the health risks associated with systemic absorption of ionic silver were low. Argyria and argyrosis are the principle observable changes associated with long-term exposure to ingestion or inhalation of high doses of metallic silver or ionisable silver compounds. The Panel noted that, in these contexts, the possible effects resulting from oral exposure to AgNPs were poorly documented.

No toxicity studies were reported on elemental silver.

The toxicity of AgNPs, mostly capped with modifying agents, is extensively studied.

Oral LD_{50} values of approximately 32, 280 and 800 mg Ag/kg bw have been reported for ionic silver (silver nitrate) in mice, rats and rabbits, respectively (Tamimi et al., 1998). For AgNPs, a dose of 5,000 mg/kg bw did not lead to mortality or acute toxic signs in mice (Maneewattanapinyo et al., 2011).

In mice, no short-term or subchronic studies on ionic silver were available. Shahare and Yaspal (2013) studied the effects of 10 mg/kg bw/day AgNPs (3–20 nm) after dosing to Swiss albino mice by gavage for 21 days and observed a decreased body weight and intestinal damage.

In rats, colloidal AgNPs (diameter of 55–60 nm) resulted in slight liver damage (affected enzymes after 28 days at a dose of 300 mg/kg bw/day (Kim et al., 2008) and after 90 days at a dose of 125 mg/kg bw/day (Kim et al., 2010). No effects were observed at 30 mg/kg bw/day. According to Kim et al. (2008, 2010), the bile duct hyperplasia observed in the liver in the 90-day study may point to a treatment-related effect of AgNPs. The Panel did not agree with this preliminary conclusion, and considered further research needed. Hadrup et al. (2012a,b,c) observed the following changes in rats after oral administration by gavage of silver acetate (9 mg ionic silver/kg bw/day) for 28 days: a decreased body weight gain, decreased thymus weight and increased liver enzymes and decreased plasma urea allantoin urine concentration and changes in the neurotransmittors. However, Van der Zande et al. (2012) observed no hepatotoxicity after daily exposure by gavage for 28 days to 90 mg/kg bw of AgNPs (18 nm, non-coated or 12 nm, PVP-coated, in diameter) or 9 mg/kg bw of silver nitrate (corresponding to 6 mg ionic silver/kg bw).

There are no data available to evaluate the *in vivo* genotoxicity of ionic silver. Concerning AgNPs, the available studies provide clear evidence of a genotoxic potential in various *in vitro* test systems. The *in vivo* oral genotoxicity studies performed provide less conclusive evidence, and do not allow a definitive assessment of the possible genotoxic hazard associated with oral exposure to AgNPs.

Overall, the Panel concluded that the available data are inadequate to evaluate the genotoxic hazard associated with the use of silver as food additive.

No studies on the carcinogenic potential of either ionic silver compounds or AgNPs have been identified. In rats, retarded growth and stained muzzles were the only effects reported following long-term exposure to ionic silver (up to 8.5 months, approximately 81 mg ionic silver/kg bw/day (Matuk et al., 1981) and 60 weeks, approximately 118 mg ionic silver/kg bw/day (Walker 1971)).

In an oral one-generation reproductive toxicity study with silver acetate in drinking water at dose levels of 0, 0.4, 4 or 40 mg silver acetate/kg bw/day (0, 0.26, 2.6 or 26 mg ionic silver/kg bw/day) in rats, a NOAEL for developmental effects (based on an increased number of pups, pup death and decreased weight gain of pups) of 0.4 mg silver acetate/kg bw/day (0.26 mg ionic silver/kg bw/day) was observed (Documentation provided to EFSA No5). The NOAEL for fertility was 4 mg silver acetate/kg bw/day (2.6 mg ionic silver/kg bw/day).

In a prenatal developmental toxicity study, developmental toxicity of ionic silver was observed when rats were dosed with silver chloride (188 mg ionic silver/kg bw/day) on GD 1–20 (Shavlovski et al., 1995). No developmental effect was observed by the same authors when rats were only dosed with silver chloride from GD 7–15. This study was only conducted at one dose level in a low number of animals and maternal toxicity was not described properly. The effects on ceruloplasmin after longer administration were emphasised by the authors.

In another prenatal developmental study (NTP, 2002) with silver acetate performed according the current guidelines at dose levels of up to 100 mg/kg bw/day (65 mg ionic silver/kg bw/day) administered from GD 6–19, a NAOEL for developmental toxicity was observed at 65 mg ionic silver/kg bw/day as the NOAEL for maternal toxicity was 6.5 mg ionic silver/kg bw/day.

The Panel noted that silver ions affected developmental toxicity at a much lower level (NOAEL 0.26 mg ionic silver/kg bw/day) in the one-generation reproductive toxicity study (Documentation provided to EFSA No5).

The Panel considered some immunotoxicity studies performed following intravenous administration but they were not evaluated because the route of exposure was considered not directly relevant to the exposure resulting from the use of silver as a food additive. The Panel noted that the outcomes of immunotoxicity studies performed with AgNPs *in vitro* and *in vivo* after oral administration were variable but always suggestive of an effect of the treatment with silver on the immune system. Inconsistencies in the outcomes (immune-stimulation or suppression) might be due to different material, doses, duration of exposure and animal or cell models used. Overall, they indicate that silver particles cytotoxicity and immunomodulatory activities are influenced by both their size and the rate of surface dissolution, leading to the release of silver ions, which seemed to be the most active form. Owing to the possibility that silver ions can be released from silver use as a food additive even if not under a nanoparticulate form, the Panel considered that the immunomodulation effects observed in studies using AgNPs are relevant for silver used as a food additive and that further investigation is warranted.

Exposure assessments of food additives under re-evaluation are carried out by the ANS Panel based on (1) MPLs set down in the EU legislation (defined as the regulatory maximum level exposure assessment scenario) and (2) usage or analytical data (defined as the refined exposure assessment scenario). It was not possible to carry out a scenario based on the MPLs set out in EU legislation, as, for all food categories, silver (E 174) is authorised according to QS. However, maximum levels of the available data were used to provide a conservative estimate scenario (noted as the *maximum level exposure assessment scenario*). With regard to the refined exposure assessment scenario, reported use levels were made available by industry only for two food categories. The Panel considers that the refined exposure assessment approach results in more realistic long-term exposure estimates because

of the underlying assumptions and the concentration data used. The Panel noted that the refined exposure estimates will not cover future changes in the level of use of silver (E 174).

From the maximum level exposure assessment, mean estimates ranged from < 0.01 to 2.6 µg/kg bw/day across all population groups. Estimates based on the high percentile (95th percentile) ranged from 0 to12 µg/kg bw/day across all population groups.

From the refined estimated exposure scenario in the brand-loyal scenario, mean exposure to silver (E 174) from its use as a food additive ranged from < 0.01 µg/kg bw/day for infants to 2.6 µg/kg bw/day in children. The high exposure to silver (E 174) ranged from 0 µg/kg bw/day for infants to 12 µg/kg bw/day in children. In the non-brand-loyal scenario, mean exposure to silver (E 174) ranged from <0.01 µg/kg bw/day for infants to 1.6 µg/kg bw/day in children. The high exposure ranged from 0 µg/kg bw/day for infants to 3.2 µg/kg bw/day in children.

The exposure from the food additive and the regular diet (ANSES, 2011) could lead to a mean intake for children around 3.5 µg/kg bw/day (non-brand-loyal scenario). On average, exposure from the food additive would represent around 30% of total dietary exposure to silver (see Table 4).

Overall, the Panel noted that there are data gaps and concerns that need to be addressed in order to conduct a risk assessment with respect to the use of silver (E 174) as food additive:

- Data from toxicity studies on elemental silver or the food additive (E 174) are lacking.
- The particle size distribution of the food additive (E 174) is unknown.
- There is evidence of the release of silver ions from elemental silver, which may be of concern. However, the extent of the release of the silver ions, which depends on multiple factors such as pH and particle size, is unknown in the case of silver (E 174) used as food additive.

5. Conclusions

The Panel concluded that the information available was insufficient to assess the safety of silver as food additive. The major issues included chemical identification and characterisation of silver E 174 (e.g. quantity of nanoparticles and release of ionic silver) and similar information on the material used in the available toxicity studies. Therefore, the Panel concluded that the relevance of the available toxicological studies to the safety evaluation of silver as a food additive E 174 could not be established.

6. Recommendation

The Panel recommended that the specifications for E 174 should include the mean particle size and particle size distribution (± SD), as well as the percentage (in number) of particles in the nanoscale (with at least one dimension below 100 nm), present in the powder form of silver (E 174) used as a food additive. The methodology applied should comply with the EFSA Guidance document (EFSA Scientific Committee, 2011), e.g. SEM or TEM.

The Panel recommended that additional data in line with the current Guidance document on evaluation of food additives (EFSA, 2012) would be required.

DOCUMENTATION PROVIDED TO EFSA

1. CIAA (Confederation of the Food and Drink Industries of the EU). Exercise on occurrence data – EFSA re-evaluation of some food colours. CIAA submission: December 2009.
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3. Eytzinger GmbH, 2011. Reply to EFSA: Call for scientific data on Silver (E 174) and Gold (E 175), used as food colours. Submitted on 27 July 2011.
4. Eytzinger GmbH, 2015. Personal communication from Eytzinger GmbH on the particle size distribution on edible Gold (E 175), 25 November 2015.
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Appendices

Appendix A – Summary of the reported use levels and concentration levels (mg/kg or mg/L as appropriate) of silver (E 174) provided by industry

FCS Category number	FCS food category	MPL	Restrictions	n	Reported use levels		Data sources/comments
					Typical mean	Highest maximum level	
05.2	Other confectionery including breath-freshening microsweets	QS	Only external coating of confectionery[(a)]	1	8	7,000	FoodDrinkEurope (representative of 2 EU countries)
05.4	Decorations, coatings and fillings, except fruit-based fillings covered by category 04.2.4	QS	Only decoration of chocolates[(a)]	1	5,000	5,000	FoodDrinkEurope
14.2.6	Spirit drinks as defined in Regulation (EC) No 110/2008	QS	Only liqueurs	1	-	-	Not taken into account (no concentration data available)

(a): With the assumption that coating and decorations represent 1% of the products (for both confectionary and chocolates).

Appendix B – Summary of total estimated exposure of silver (E 174) from their use as food additives for the maximum level exposure scenario and the refined exposure assessment scenarios per population group and survey: mean and high level (mg/kg bw/day)

	Number of subjects	Maximum level scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level
Infants							
Bulgaria (NUTRICHILD)	659	5.9E-04	0.0E+00	5.9E-04	0.0E+00	2.9E-04	0.0E+00
Germany (VELS)	159	3.1E-03	2.5E-02	2.9E-03	2.5E-02	2.4E-03	2.5E-02
Denmark (IAT 2006_07)	826	2.4E-03	1.0E-02	2.2E-03	8.4E-03	1.3E-03	6.9E-03
Finland (DIPP_2001_2009)	500	9.8E-06	0.0E+00	9.8E-06	0.0E+00	8.8E-06	0.0E+00
United Kingdom (DNSIYC_2011)	1366	4.0E-03	2.9E-02	4.0E-03	2.9E-02	3.8E-03	2.5E-02
Italy (INRAN_SCAI_2005_06)	12	6.1E-03		6.1E-03		6.1E-03	
Toddlers							
Belgium (Regional_Flanders)	36	6.8E-02		6.2E-02		5.8E-02	
Bulgaria (NUTRICHILD)	428	1.8E-02	1.2E-01	1.7E-02	1.0E-01	7.4E-03	5.2E-02
Germany (VELS)	348	4.4E-02	1.1E-01	3.9E-02	1.1E-01	2.4E-02	7.0E-02
Denmark (IAT 2006_07)	917	3.8E-02	1.3E-01	3.5E-02	1.1E-01	1.7E-02	6.5E-02
Spain (enKid)	17	1.4E-02		1.0E-02		1.0E-02	
Finland (DIPP_2001_2009)	500	3.1E-03	1.4E-02	3.1E-03	1.4E-02	1.0E-03	8.3E-03
United Kingdom (NDNS-RollingProgrammeYears1-3)	185	3.2E-02	1.1E-01	3.0E-02	1.1E-01	1.7E-02	6.1E-02
United Kingdom (DNSIYC_2011)	1314	1.6E-02	7.5E-02	1.5E-02	7.3E-02	1.3E-02	6.5E-02
Italy (INRAN_SCAI_2005_06)	36	1.0E-02		9.9E-03		9.2E-03	
Netherlands (VCP_kids)	322	7.5E-02	2.1E-01	6.7E-02	1.8E-01	4.1E-02	1.4E-01
Children							
Austria (ASNS_Children)	128	3.7E-02	1.1E-01	3.4E-02	1.1E-01	2.5E-02	8.6E-02
Belgium (Regional_Flanders)	625	6.0E-02	1.6E-01	5.6E-02	1.5E-01	3.8E-02	1.2E-01
Bulgaria (NUTRICHILD)	433	2.6E-02	1.3E-01	2.5E-02	1.3E-01	1.4E-02	8.9E-02
Czech Republic (SISP04)	389	6.0E-02	2.5E-01	5.9E-02	2.5E-01	2.3E-02	1.2E-01
Germany (EsKiMo)	835	5.9E-02	1.6E-01	5.2E-02	1.5E-01	3.6E-02	1.1E-01
Germany (VELS)	293	5.4E-02	1.4E-01	4.7E-02	1.3E-01	3.2E-02	8.3E-02
Denmark (DANSDA 2005-08)	298	6.0E-02	1.4E-01	5.3E-02	1.3E-01	2.7E-02	7.3E-02
Spain (enKid)	156	2.9E-02	1.2E-01	2.8E-02	1.2E-01	2.0E-02	6.9E-02
Spain (NUT_INK05)	399	2.4E-02	8.1E-02	2.3E-02	7.7E-02	1.6E-02	6.6E-02
Finland (DIPP_2001_2009)	750	1.1E-01	4.6E-01	1.1E-01	4.6E-01	1.3E-02	5.8E-02
France (INCA2)	482	3.1E-02	9.3E-02	2.8E-02	8.6E-02	2.2E-02	8.1E-02
United Kingdom (NDNS-RollingProgrammeYears1-3)	651	3.5E-02	1.3E-01	3.3E-02	1.2E-01	2.0E-02	6.5E-02
Greece (Regional_Crete)	838	1.0E-02	4.7E-02	1.0E-02	4.7E-02	6.7E-03	3.2E-02
Italy	193	1.6E-02	7.9E-02	1.6E-02	7.9E-02	1.5E-02	6.7E-02

	Number of subjects	Maximum level scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level
(INRAN_SCAI_2005_06)							
Latvia (EFSA_TEST)	187	3.3E-02	1.2E-01	3.3E-02	1.2E-01	1.9E-02	8.3E-02
Netherlands (VCP_kids)	957	7.9E-02	1.9E-01	7.0E-02	1.8E-01	4.1E-02	1.2E-01
Netherlands (VCPBasis_AVL2007_2010)	447	6.5E-02	1.7E-01	5.8E-02	1.5E-01	3.3E-02	1.0E-01
Sweden (NFA)	1473	5.1E-02	1.6E-01	5.0E-02	1.6E-01	1.1E-02	5.5E-02
Adolescents							
Austria (ASNS_Children)	237	1.3E-02	5.7E-02	1.3E-02	5.2E-02	1.0E-02	4.4E-02
Belgium (Diet_National_2004)	576	2.4E-02	8.5E-02	2.3E-02	7.7E-02	1.9E-02	7.0E-02
Cyprus (Childhealth)	303	1.2E-02	4.6E-02	1.1E-02	4.4E-02	9.9E-03	3.8E-02
Czech Republic (SISP04)	298	2.9E-02	1.6E-01	2.8E-02	1.5E-01	1.1E-02	6.6E-02
Germany (National_ Nutrition_Survey_II)	1011	2.0E-02	1.1E-01	1.9E-02	1.0E-01	7.6E-03	4.2E-02
Germany (EsKiMo)	393	4.4E-02	1.4E-01	3.9E-02	1.1E-01	2.8E-02	8.3E-02
Denmark (DANSDA 2005-08)	377	3.4E-02	9.1E-02	3.1E-02	8.8E-02	1.6E-02	5.2E-02
Spain (AESAN_FIAB)	86	2.7E-02	1.1E-01	2.7E-02	1.1E-01	7.2E-03	3.8E-02
Spain (enKid)	209	1.5E-02	7.6E-02	1.5E-02	6.4E-02	7.0E-03	3.5E-02
Spain (NUT_INK05)	651	1.3E-02	5.8E-02	1.3E-02	5.7E-02	8.2E-03	4.1E-02
Finland (NWSSP07_08)	306	8.1E-02	3.3E-01	8.1E-02	3.3E-01	6.5E-03	3.2E-02
France (INCA2)	973	1.8E-02	6.0E-02	1.7E-02	5.6E-02	1.3E-02	4.8E-02
United Kingdom (NDNS-RollingProgrammeYears1-3)	666	2.1E-02	7.6E-02	2.0E-02	7.0E-02	1.4E-02	4.7E-02
Italy (INRAN_SCAI_2005_06)	247	7.5E-03	3.1E-02	7.3E-03	3.1E-02	7.0E-03	3.0E-02
Latvia (EFSA_TEST)	453	1.4E-02	7.4E-02	1.4E-02	7.4E-02	1.3E-02	6.6E-02
Netherlands (VCPBasis_AVL2007_2010)	1142	3.5E-02	1.1E-01	3.2E-02	1.0E-01	1.8E-02	5.9E-02
Sweden (NFA)	1018	3.8E-02	1.4E-01	3.7E-02	1.4E-01	9.6E-03	5.0E-02
Adults							
Austria (ASNS_Adults)	308	8.5E-03	3.8E-02	8.3E-03	3.8E-02	7.0E-03	3.3E-02
Belgium (Diet_National_2004)	1292	1.2E-02	4.5E-02	1.2E-02	4.4E-02	9.9E-03	4.1E-02
Czech Republic (SISP04)	1666	3.6E-03	2.2E-02	3.6E-03	2.2E-02	2.5E-03	1.8E-02
Germany (National_ Nutrition_Survey_II)	10419	1.6E-02	7.4E-02	1.6E-02	7.1E-02	5.7E-03	3.2E-02
Denmark (DANSDA 2005-08)	1739	1.6E-02	5.2E-02	1.5E-02	4.9E-02	6.9E-03	2.5E-02
Spain (AESAN)	410	5.6E-03	2.8E-02	5.5E-03	2.8E-02	3.8E-03	2.3E-02
Spain (AESAN_FIAB)	981	1.3E-02	4.0E-02	1.3E-02	4.0E-02	3.3E-03	1.9E-02
Finland (FINDIET2012)	1295	2.9E-02	1.7E-01	2.9E-02	1.7E-01	4.7E-03	2.5E-02
France (INCA2)	2276	6.1E-03	2.9E-02	5.8E-03	2.5E-02	4.3E-03	2.1E-02
United Kingdom (NDNS-RollingProgrammeYears1-3)	1266	8.2E-03	3.3E-02	7.9E-03	3.2E-02	5.9E-03	2.7E-02
Hungary (National_Repr_Surv)	1074	3.4E-03	2.0E-02	3.4E-03	2.0E-02	3.3E-03	2.0E-02
Ireland (NANS_2012)	1274	7.9E-03	3.4E-02	7.5E-03	3.2E-02	6.0E-03	2.6E-02

	Number of subjects	Maximum level scenario		Brand-loyal scenario		Non-brand-loyal scenario	
		Mean	High level	Mean	High level	Mean	High level
Italy (INRAN_SCAI_2005_06)	2313	1.9E-03	1.1E-02	1.9E-03	1.1E-02	1.6E-03	9.9E-03
Latvia (EFSA_TEST)	1271	6.3E-03	3.3E-02	6.3E-03	3.2E-02	4.9E-03	3.1E-02
Netherlands (VCPBasis_AVL2007_2010)	2057	1.3E-02	4.8E-02	1.2E-02	4.5E-02	7.7E-03	3.4E-02
Romania (Dieta_Pilot_Adults)	1254	3.8E-03	1.9E-02	3.7E-03	1.9E-02	2.5E-03	1.4E-02
Sweden (Riksmaten 2010)	1430	1.1E-02	5.0E-02	1.1E-02	4.8E-02	4.9E-03	2.4E-02
The elderly							
Austria (ASNS_Adults)	92	3.0E-03	1.2E-02	2.9E-03	1.2E-02	2.9E-03	1.2E-02
Belgium (Diet_National_2004)	1215	5.9E-03	2.8E-02	5.8E-03	2.7E-02	4.6E-03	2.4E-02
Germany (National_ Nutrition_Survey_II)	2496	4.8E-03	2.4E-02	4.8E-03	2.2E-02	2.6E-03	1.7E-02
Denmark (DANSDA 2005-08)	286	7.9E-03	3.0E-02	7.1E-03	2.5E-02	4.0E-03	1.6E-02
Finland (FINDIET2012)	413	8.0E-03	4.5E-02	7.9E-03	3.5E-02	1.3E-03	7.8E-03
France (INCA2)	348	2.9E-03	1.1E-02	2.9E-03	1.1E-02	1.3E-03	8.0E-03
United Kingdom (NDNS-RollingProgrammeYears1-3)	305	6.0E-03	2.1E-02	5.9E-03	2.1E-02	3.1E-03	1.5E-02
Hungary (National_Repr_Surv)	286	1.6E-03	7.4E-03	1.6E-03	7.4E-03	1.1E-03	6.4E-03
Ireland (NANS_2012)	226	1.9E-03	1.2E-02	1.8E-03	1.2E-02	1.6E-03	1.1E-02
Italy (INRAN_SCAI_2005_06)	518	9.1E-04	4.4E-03	8.8E-04	4.3E-03	6.9E-04	3.7E-03
Netherlands (VCPBasis_AVL2007_2010)	173	6.4E-03	2.6E-02	5.9E-03	2.5E-02	4.2E-03	2.3E-02
Netherlands (VCP-Elderly)	739	7.5E-03	2.7E-02	6.9E-03	2.6E-02	5.3E-03	2.3E-02
Romania (Dieta_Pilot_Adults)	128	2.4E-03	1.3E-02	2.3E-03	1.1E-02	8.6E-04	5.0E-03
Sweden (Riksmaten 2010)	367	4.7E-03	2.4E-02	4.5E-03	2.3E-02	3.0E-03	1.7E-02

Appendix C – References of the studies with capped material considered by the Panel

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ABBREVIATIONS

ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
ALP	alkaline phosphatase
ALT	alkaline transaminase
AST	aspartate transaminase
AgNPs	silver nanoparticles
BUN	blood urea nitrogen
Bw	body weight
CEF	EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
DLLME	dispersive liquid-liquid microextraction
DLS	dynamic light scattering
DNA	deoxyribonucleic acid
EC	European Commission
EINECS	European Inventory of Existing Commercial Chemical Substances
EDX	energy dispersive X-ray
ENM	engineered nanomaterials
FAO	Food and Agriculture Organization of the United Nations
FCS	Food Categorisation System
FDA	US Food and Drug Administration
FDE	Food Drink Europe
GI	gastrointestinal
GLP	good laboratory practice
GFAAS	graphite furnace atomic absorption spectrometry
HAADF-STEM	high-angle annular dark-field scanning transmission electron microscopy
ICP	inductively coupled mass
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	median lethal dose
MN	micronuclei
MPL	maximum permitted level
MS	mass spectrometry
MTT	methyltetrazolium
NCE	normochromatic erythrocyte
NOAEL	no-observed-adverse-effect Level
OECD	Organisation for Economic Co-operation and Development

OES	optical emission spectrometry
PCE	polychromatic erythrocyte
PVP	Polyvinylpyrrolidone
QS	quantum satis
ROS	reactive oxygen species
SCE	sister chromatid exchange
SCF	Scientific Committee for Food
SEM	scanning electron microscopy
SP	single particle
TEM	transmission electron microscopy
WHO	World Health Organization