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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Interim Position for Toxicological End-points for Silver

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Action Required:
The Risk Assessment and Science Support Branch (RASSB) was asked to prepare interim end-points for silver compounds based on existing toxicological information.

Background Information:
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.

In June of 1999, the Health Effects Division's (HIARC) met to discuss the adequacy of the toxicology database for silver. Data were referenced from the 1993 Reregistration Eligibility Decision (RED) document, and were based solely upon open scientific literature. HIARC concluded that the studies cited in the RED were inadequate for hazard identification and risk assessment.

On September 8, 2004, members of the Antimicrobials Division Toxicity Endpoint Committee (ADTC) met again to discuss toxicology issues with respect to silver. ADTC discussed this issue using the available information on the hazard (updated database) and the chemistry of the silver compounds under consideration. The ADTC concluded that chemically, zeolite-based silver active ingredients were not similar to salts of silver, and that hazards would need to be considered separately for each silver compound. However, for purposes of hazard characterization and endpoint selection for risk assessments involving elemental silver and silver salts, the ADTC concluded that silver salts can be treated together as a class. Once internalized to the body, the compound of interest is ionic silver, which is common to the silver salts. Therefore, one toxicology dataset can represent the hazard for the silver salts. As the silver RED document and the available open scientific literature are insufficient to characterize the hazard of silver and silver salts, registrants seeking uses for silver and silver salts will need to address toxicology data requirements when submitting applications to the Antimicrobials Division. The Risk Assessment and Science Support Branch (RASSB) was asked to prepare interim end-points for risk assessment before the toxicological data are available.

Interim end-points Decision:

The ADTC also noted that any new silver and other related compounds will be reviewed on a case-by-case basis to determine whether the compound is similar to an existing class (i.e. silver salts, silver zeolites, etc.) or represents a new class of chemical.

For Silver Salts.

There are several regulatory agencies that set regulatory end-points for silver based on argyria formation after silver exposure (**Table 1**). The Agency is concerned that there are no developmental or reproductive toxicity studies available for silver. There is evidence demonstrating the deposition of silver in the brains of offspring exposed to silver. There are no neurotoxicity data on silver, which is of concern based on evidence of silver localization in specific

brain regions for both adult experimental animals as well as offspring. In addition, there is no chronic long term study available to evaluate the potential long-term exposure risks.

For oral exposure route, RASSB uses the drinking water Secondary Maximum Contaminant Level (SMCL) level of 0.1 mg/L (0.003 mg/kg/day) based on skin discoloration and graying of the whites of eyes (Argyria), and applied an additional safety factor of 3 to address the residual uncertainty associated with the missing reproductive, developmental, neurotoxicity and chronic toxicology studies. A safety factor of 3 instead of 10 is used based on historical data for silver.

$$\text{Oral Interim Endpoint} = \frac{0.003 mg/kg/day}{3} = 0.001 mg/kg/day$$

For Inhalation Exposure, RASSB decide to use the on OSHA 8-hour TWA of 0.01 mg/m^3 (0.001 mg/kg/day) based on argyria and applied an additional safety factor of 3x to address the residual uncertainty associated with the missing reproductive, developmental, neurotoxicity and chronic toxicology studies. A safety factor of 3 instead of 10 is used based on historical data for silver.

$$\text{Inhalation Interim Endpoint} = \frac{0.001 mg/kg/day}{3} = 0.0003 mg/kg/day$$

For Dermal Exposure, silver ion tends to bind to the skin and do not penetrate the skin to cause systemic effects. Skin discoloration is the only concern for silver exposure through the dermal route. The dermal risk assessment for silver uses the drinking water SMCL level of 0.1 mg/L (0.003 mg/kg/day), without any extra safety factor.

$$\text{Dermal Interim Endpoint} = \frac{0.003 mg/kg/day}{1} = 0.003 mg/kg/day$$

For Silver Compounds Other Than Silver Salts:

ADTC noted that Milliken Chemical has the most complete toxicology database for its registration of silver sodium hydrogen zirconium phosphate for food contact, water contact, and non-food uses in treated articles and ADTC selected toxicological end-points based on the Milliken's toxicology database (See **Table 2**). The ADTC has proposed to review other silver zeolites and silver compounds on a case by case basis.

cc: Chemical File
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Table 1. Federal Regulation and Advisories for Silver:

Regulation and Advisories	Description	Level	Converted Level in mg/kg/day
Water			
Based on Drinking Water SMCL[1]	Skin discoloration; graying of the White of Eyes (Argyria)	0.1 mg/L	0.003 mg/kg/day [2]
Based on Oral RfD of IRIS	Based on 2- to 9-Year Human i.v. Study (Gaul and Staud, 1935). LOAEL: 1 g (total dose); converted to an oral dose Of 0.014 mg/kg/day. No NOAEL was identified	0.005 mg/kg/day	0.005 mg/kg/day
Air			
Based on OSHA 8-hour TWA [3]	Argyria	0.01mg/m^3 (metal, dust and fume)	0.001 mg/kg/day [4]
Based on ACGIH TLV	Relied on a publication by Pillsbury and Hill (1939, as cited in ACGIH 1986/EX.1-3, P.529), which stated an accumulated intake of from 1 to 5 grams of silver would generalized argyria.	For Soluble Silver Compounds 0.01 mg/m^3 For Silver Metal 0.1mg/m^3	For Soluble Silver Compounds 0.001 mg/kg/day[4] For Silver Metal 0.01 mg/kg/day[4]

Note:

1) The Agency has established National Secondary Maximum Contaminant Level (SMCL) for silver at a level of water not exceed 0.10 mgs /L of drinking water (0.10 mg/L). The SMCL means the maximum permissible level of a contaminant in water which is delivered to the free flowing outlet of the ultimate user of public water system. Contaminants added to the water under circumstances controlled by the user, except those resulting from corrosion of piping and plumbing caused by water quality, are excluded from this definition.
2) The oral drinking water level was converted to a corresponding dose assuming human body weight of 70 kg and water consumption of 2 L/day.
3) The Occupational Safety and Health Administration (OSHA) limits silver in workplace air to 0.01 milligrams per cubic meter (0.01 mg/m^3) for an 8-hour workday, 40-hour workweek.
4) The air concentration was converted to corresponding daily dose of mg/kg/day based on assumptions of inhalation rate of 20m^3/day, work 8 hours per day, and human body weight of 70kg.

Table 2. The Toxiological End-points - Silver Sodium Hydrogen Zirconium Phosphate (A (A zeolite-type chemical by Milliken Chemical)

Exposure Scenario	Dose Used in Risk Assessment, UF	LOC for Risk Assessment	Study and Toxicological Endpoints
Acute Dietary (Females 13 - 50)			No endpoint was identified in the toxicology database for acute dietary risk. This risk assessment is not required.
Acute Dietary (General population, including infants/children)			No endpoint was identified in the toxicology database for acute dietary risk. This risk assessment is not required.
Chronic Dietary (all populations)	oral NOAEL = 400 mg/kg/day **Chronic cPAD =1.3** mg/kg/day UF = 300 (10x interspecies, 10x intraspecies, 3x for use of a subchronic NOAEL)	FQPA SF = 1x **cPAD** = chronic RfD / FQPA SF **cPAD = 1.3 mg/kg/day**	Subchronic (90-day) oral toxicity study in dogs (MRID 45769401) NOAEL of 400 mg/kg/day, based on chronic granulomatous inflammation of the liver accompanied by vacuolization and necrosis at a dose of 700 mg/kg/day.
Short- and Intermediate-Term Incidental Oral	oral NOAEL = 400 mg/kg/day	MOE = 100 (residential)	Subchronic (90-day) oral toxicity study in dogs (MRID 45769401) NOAEL of 400 mg/kg/day, based on chronic granulomatous inflammation of the liver accompanied by vacuolization and necrosis at a dose of 700 mg/kg/day.
Short- and Intermediate-term Dermal	Oral NOAEL = 400 mg/kg/day	MOE = 100 (residential) MOE = 100 (occupational)	Subchronic (90-day) oral toxicity study in dogs (MRID 45769401) NOAEL of 400 mg/kg/day, based on chronic granulomatous inflammation of the liver accompanied by vacuolization and necrosis at a dose of 700 mg/kg/day.
Short- and Intermediate-Term Inhalation	Oral NOAEL = 400 mg/kg/day	MOE = 1000 (residential) MOE = 100 (occupational)	Subchronic (90-day) oral toxicity study in dogs (MRID 45769401) NOAEL of 400 mg/kg/day, based on chronic granulomatous inflammation of the liver accompanied by vacuolization and necrosis at a dose of 700 mg/kg/day.

Dermal absorption assumed to be 100% in the absence of specific dermal absorption data.
No inhalation data other than an acute inhalation toxicity study were available for silver sodium hydrogen zirconium phosphate. Thus, an oral endpoint was chosen for inhalation risk assessment with a Margin of Exposure of 1000 (10x interspecies, 10x intraspecies, and 10 x for extrapolation from an oral to inhalation endpoint.