

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ANTIMONY AND COMPOUNDS IN THE UNITED STATES

Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 mg/kg (ppm), but these levels vary by location. It can be transported into streams and waterways from natural weathering of soil, as well as from anthropogenic sources. Antimony enters the environment during the mining and processing of antimony-containing ores and in the production of antimony metal, alloys, antimony oxide, and combinations of antimony with other substances. Antimony was mined in the United States; however, the last mine closed in 2001. Impure antimony ore and metal are imported into the United States from other countries for processing. Small amounts of antimony are released into the environment by incinerators and coal-burning power plants. Studies indicate that antimony is retained in the soil through adsorption and can sorb onto clay minerals, oxides, and hydroxides in the soil and aquatic sediment.

Antimony is predominantly in the +5 oxidation state in both aerobic freshwater and seawater. These waters also contain antimony in the +3 oxidation state to a lesser extent. Trivalent antimony is the dominant oxidation state of antimony in anaerobic environments. The predominant trivalent species in the environment is antimony trihydroxide ($\text{Sb}(\text{OH})_3$) and the predominant pentavalent species is hexahydroxoantimonate ($\text{Sb}(\text{OH})_6^-$), as predicted by thermodynamic calculations.

Antimony can be reduced and methylated by microorganisms in anaerobic sediment, releasing volatile methylated antimony compounds into the water. Multiple microorganisms have been found to methylate antimony in the soil and water and other anaerobic environments.

The general population is exposed to low levels of antimony from ingestion of food and drinking water and possibly by inhalation of particulate matter containing antimony in ambient air. Occupational exposures of antimony may occur at smelters, coal-fired plants, and refuse incinerators that process or release antimony.

2.2 SUMMARY OF HEALTH EFFECTS

Antimony and its compounds are among the oldest known remedies in the practice of medicine and they have been used to treat a variety of illnesses over the last 600 years. Currently, antimony compounds are used to treat the parasitic disease leishmaniasis. Toxic side effects in humans following intraperitoneal,

2. RELEVANCE TO PUBLIC HEALTH

intravenous, or intramuscular injection of an antimony-containing drug have been reported, including altered electrocardiograms (EKGs), vomiting, diarrhea, and joint and/or muscle pain. These side effects are more frequently observed following administration of trivalent antimony compounds, especially antimony potassium tartrate or antimony sodium tartrate; side effects have also been found in humans administered pentavalent organic compounds such as sodium antimony gluconate or meglumine antimoniate.

Adverse health effects have also been observed in humans and animals following inhalation, oral, or dermal exposure to antimony and antimony compounds. These studies predominantly assessed the toxicity of trivalent antimony compounds, particularly antimony trioxide and antimony potassium tartrate. In both humans and animals, the respiratory tract is the predominant target of antimony toxicity following inhalation exposure, and a systematic review of the data (see Appendix B for additional information) supports the conclusion that antimony is presumed to cause respiratory health effects in humans. The lung is the primary target of toxicity within the respiratory tract, and effects are observed following acute-, intermediate-, and chronic-duration exposure. In antimony workers, pneumoconiosis and clinical signs such as coughing and laryngitis have been reported. A relationship between exposure level and effect cannot be established from these data because the workers were also exposed to other compounds, including arsenic oxide, iron oxide, hydrogen chloride, and hydrogen sulfide. In laboratory animals, the lung effects include the accumulation of antimony particles in the lungs, increases in alveolar/intra-alveolar macrophages, decreases in antimony lung clearance times, chronic interstitial inflammation, and interstitial fibrosis. Lung effects have been found in rats, mice, and rabbits following exposure to antimony trioxide, antimony trisulfide, and antimony ore; lung effects have also been observed in laboratory animals following exposure to stibine gas. Intermediate- and chronic-duration studies demonstrated that pulmonary damage can occur postexposure due to the persistence of the antimony trioxide in the lung. At the end of a 13-week or 1-year exposure to antimony trioxide, histological alterations in the lungs were limited to increases in alveolar/intra-alveolar macrophages; however, after 27-week or 1-year recovery periods, respectively, interstitial inflammation and fibrosis were observed. Other respiratory effects that have been observed in some studies include squamous metaplasia of the epiglottis and hyperplasia of the nasal respiratory epithelium. The lowest lowest-observed-adverse-effect levels (LOAELs) for respiratory tract effects following acute-, intermediate-, and chronic-duration exposures are 12 mg Sb/m³ as antimony trioxide, 4.11 mg Sb/m³ as antimony trioxide, and 1.6 mg Sb/m³ as antimony trioxide, respectively.

2. RELEVANCE TO PUBLIC HEALTH

Cardiovascular effects, especially myocardial damage and alterations in EKGs, have been observed in humans and animals exposed to antimony. Based on the systematic review of the available data (Appendix B), ATSDR concluded that antimony is suspected to cause cardiovascular health effects, specifically myocardial and EKG alterations, in humans. In workers exposed to antimony trisulfide dust, EKG alterations were found in about 50% of the workers. A small number of animal studies included EKG readings; these studies reported alterations in rats, rabbits, and dogs exposed to airborne antimony trisulfide. No alterations were observed in guinea pigs or pigs exposed to airborne antimony trioxide for intermediate or chronic durations. These findings are supported by reports of altered EKG readings (particularly prolongation of the QT interval) in individuals exposed to repeated injections of antimony and in experimental studies in laboratory animals injected with trivalent or pentavalent antimony compounds.

Historically, antimony has been known for its emetic properties. Gastrointestinal tract irritation is a presumed health effect of antimony in humans based on the systematic review of occupational exposure studies and inhalation and oral exposure studies in laboratory animals. Abdominal pain, vomiting, nausea, and ulcers have been observed in antimony workers. Gastrointestinal effects have also been observed in humans receiving intramuscular injections of antimony. Vomiting has also been observed in dogs following acute oral exposure and chronic inflammation and/or ulceration was observed in the forestomach of mice following acute oral exposure to antimony potassium tartrate or chronic inhalation exposure to antimony trioxide. Overt signs of gastrointestinal irritation or histological alterations of the gastrointestinal tract have not been observed in numerous inhalation or oral exposure studies in rats.

There are some data to indicate that antimony decreases blood glucose levels following intermediate or chronic oral exposure in rats, with supporting data from an intermediate-duration study finding decreased blood glucose levels in rats administered intramuscular injections of organic pentavalent compounds. Based on the systematic review, it was categorized as a suspected health effect in humans.

The developmental toxicity of antimony has not been extensively evaluated in humans or animals. Decreases in growth have been reported in the infants of female antimony workers; interpretation of the results of this study is limited by the lack of study details, particularly regarding the control group, antimony concentrations in the facility, type of work the women performed, and potential exposure to other compounds. Studies in animals support the findings of this occupational exposure study. Decreases in pup growth were observed in the offspring of rats orally exposed to antimony trichloride during gestation and lactation, and decreases in birth weight or fetal weight were observed in rats administered

2. RELEVANCE TO PUBLIC HEALTH

organic pentavalent antimony compounds via subcutaneous or intramuscular injection or administered antimony trichloride via intramuscular injection. Antimony does not appear to result in external or skeletal abnormalities in rats following oral or parenteral administration. Based on these data, developmental toxicity is a suspected human health effect (see Appendix B for additional information). Exposure to antimony during gestation and/or lactation and post-weaning exposure has resulted in impaired vasomotor response to 1-noradrenaline, 1-isoprenaline, and acetylcholine in 30- and 60-day-old rat pups.

Other health effects that have been observed in animals orally exposed to higher doses of antimony include hepatocellular vacuolization, hematological alterations including decreases in red blood cell counts and hemoglobin levels, and histological alterations in the thyroid.

Dermatosis and ocular irritation have been reported in workers exposed to airborne antimony. The dermatitis was seen more often during the summer months and in workers exposed to high temperatures. It is probably the result of antimony being dissolved in sweat and penetrating the sweat glands. In general, dermal effects have not been observed in animal studies. Animal studies do provide support for antimony being considered an ocular irritant. Eye irritation has been reported in animals exposed to stibine gas and following instillation of antimony thioantimonate into rabbit eyes. Additionally, increases in corneal opacities and cataracts have been observed in animals repeatedly exposed to airborne antimony trioxide.

Two occupational exposure studies examining carcinogenicity of antimony have found increases in lung cancer deaths. Mixed results have been found in chronic inhalation studies in rats. Increases in lung neoplasms were observed in rats exposed to 4.2 or 36 mg Sb/m³ as antimony trioxide for approximately 1 year. A third 1-year exposure study (followed by a 1-year recovery) did not find lung neoplasms in rats exposed to 3.8 mg Sb/m³. A 2-year inhalation study conducted by the National Toxicology Program found increases in the incidence of alveolar/bronchiolar adenomas in rats and alveolar/bronchiolar adenomas and carcinomas in mice. No increases in tumors were found in rats or mice following lifetime oral exposure to antimony potassium tartrate. The International Agency for Research on Cancer categorized antimony trioxide in group 2B (possibly carcinogenic to humans) and antimony trisulfide in group 3 (not classifiable as to its carcinogenicity to humans). The NTP and EPA have not classified the carcinogenicity of antimony.

2. RELEVANCE TO PUBLIC HEALTH

2.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 2-1, inhalation MRLs have been derived for acute-, intermediate-, and chronic-duration exposure to antimony and oral MRLs have been derived for acute- and intermediate-duration exposure to antimony. Refer to Section 3.6.2 and Appendix A for detailed information regarding MRL derivation.

2. RELEVANCE TO PUBLIC HEALTH

Table 2-1. Minimal Risk Levels (MRLs) for Antimony^a

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure					
Acute	0.001 mg Sb/m ³	Squamous metaplasia of the epiglottis of mice exposed to ≥12 mg Sb/m ³	BMCL _{HEC} of 0.035 mg Sb/m ³	30 ^b	NTP 2016
Intermediate	Adopted the acute-duration inhalation MRL of 0.001 mg Sb/m ³				
Chronic	0.0003 mg Sb/m ³	Chronic lung inflammation in female rats	BMCL _{HEC} of 0.008 mg Sb/m ³	30 ^b	Newton et al. 1994
Oral exposure					
Acute	1 mg Sb/kg/day	Focal ulceration of the forestomach in mice	NOAEL of 99 mg Sb/kg/day	100 ^c	NTP 1992
Intermediate	0.0006 mg Sb/kg/day	Decreased serum glucose levels in female rats	NOAEL of 0.064 mg Sb/kg/day	100 ^c	Poon et al. 1998
Chronic	Insufficient data for derivation of an MRL				

^aThe respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.

^bUncertainty factors: 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability.

^cUncertainty factors: 10 for extrapolation from animals to humans and 10 for human variability.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; LOAEL = lowest observed adverse effect level