Antimony Trioxide
[CAS No. 1309-64-4]

Brief Review of Toxicological Literature

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Chemical Name: Antimony Trioxide

CAS RN: 1309-64-4

Formula: Sb_2O_3

Basis for Nomination:

Antimony trioxide was nominated by the National Institute of Environmental Health Sciences for chronic toxicity, cardiotoxicity and carcinogenicity studies due to the potential for substantial human exposure in occupational settings and lack of adequate two-year exposure carcinogenicity studies. Additional studies of antimony trioxide are of interest, in lieu of studies with antimony trisulfide or another antimony compound, considering the higher volume of use and magnitude of human exposure, and the lack of two-year exposure carcinogenicity studies for any antimony compound by any route of administration.

Antimony trisulfide was nominated to the NTP by the National Cancer Institute in 2002 for carcinogenicity studies (http://ntp.niehs.nih.gov/ntpweb/index.cfm?objectid=25BEBA08-BDB7-CEBA-FC56EAD78615ADCF). Subsequent to the nomination review process, the NTP concluded that antimony trisulfide should not be studied further at this time for the following reasons: 1) antimony trisulfide does not appear to represent a major form of antimony to which humans are exposed; 2) carcinogenicity studies of antimony trisulfide is unlikely to lead to a sufficient understanding of the carcinogenicity hazard for antimony compounds as a group; and 3) there is concern regarding the safe handling of pure antimony trisulfide in experimental settings due to its flammable/combustible nature.

There is potential for occupational exposure to antimony trisulfide and antimony trioxide via inhalation, during processing and packaging of antimony compounds and during processing and smelting of antimony ores, and limits for workplace exposure are set for antimony compounds as a group (0.5 mg Sb/m^3). According to NIOSH estimates (NOES, 1981-1983), approximately 210,000 industrial workers were potentially exposed to antimony trioxide, compared to approximately 27,000 for antimony trisulfide.

The International Agency for Research on Cancer (IARC) lists antimony trisulfide as group 3, *not classifiable as to its carcinogenicity to humans*, and antimony trioxide as group 2B, *possibly carcinogenic to humans.* Since the IARC evaluation in 1989, additional studies with antimony trioxide have shown inconclusive or dissimilar results. Results of epidemiological studies have been inconclusive, mostly confounded by co-exposures to other agents. A chronic inhalation study (one-year exposure followed by a one-year observation period) supported by the Antimony Oxide Industry Association (AOIA) as part of a voluntary testing agreement with the U.S. EPA, showed no differences in tumor incidences among rats exposed to antimony trioxide and controls (Newton et al., 1994). Furthermore, a nose-only inhalation toxicity study in rats showed no developmental effects of antimony trioxide (Serex, 2004).

Though the Negotiated Testing Agreement (NTA) between the U.S. EPA and the AOIA specified a chronic oncogenicity study was to be conducted (U.S. EPA, 1983, Fed. Reg. 48: 39978-82), it appears a 2 year study was not performed. All testing requirements have been completed in accordance with the NTA and the status is listed as "closed", indicating that no further testing will be done by the antimony industry under this agreement (http://www.epa.gov/opptintr/chemtest/antimon1.htm). The Newton et al. (1994) study was the principal study used by the U.S. EPA for deriving an inhalation reference concentration for antimony trioxide; however, a carcinogenicity assessment has not been done under the Integrated Risk Information System (IRIS) program (http://www.epa.gov/iris/subst/0676.htm).

Much of the information contained in this document was extracted from the National Research Council (2000) report "*Toxicological Risks of Selected Flame Retardant Chemicals*". The IRIS record for antimony trioxide briefly discusses the inhalation toxicology database for antimony trioxide including limitations of existing studies and remaining uncertainties.

A. Chemical Information

Molecular Identification

Chemical Name: Antimony trioxide
CAS RN: 1309-64-4
Synonyms: A1530, A1582, a1588 lp, Antimonious oxide, Antimony oxide, Antimony (III) oxide, Antimony white, Antimony sesquioxide, Antimony Peroxide, AP 50, bianitmony trioxide, Chemetron fire shield, CI 77052, C.I. Pigment White 11, Dechlorane a-o, Diantimony trioxide, Exitelite, Flowers of antimony, Nyacol a 1530, Senarmontite, Valentinite, Weisspiessglanz
Trade Names: FireShield®, Microfine®, Montana Brand, Thermoguard®, Timonox, TMS®, Trutint®, Ultrafine®, White Star
Hill Formula: O3Sb2 **Line Formula:** $[Sb^{+3}]_2$ $[O^{-2}]_3$ **Smiles Notation:** [Sb]O2
Molecular Weight: 291.5
Purity of Commercial Products: 99.2-99.5%
Additives in Commercial Products: Not available
Impurities in Commercial Products: Trace impurities such as arsenic, copper, iron, lead, and nickel (HSDB, 2002); generally contains up to 0.3% of both lead and arsenic contaminants on a weight basis (HDP User Group International, Inc., 2005)
Mammalian Metabolites: Not available
Biodegradation Products: Not available
Environmental Transformation
Air: As an aerosol, antimony is oxidized to antimony trioxide by reaction with atmospheric oxidants. Antimony trioxide particles do not undergo change in chemical composition, particle size, or morphology after emission; however, a surface coating of sulfate may form (ATSDR, 1992).
Water: Antimony trioxide suspensions strongly absorb ultraviolet radiation below 325 nm and become darker in color. The process is reversible when light is removed (white color slowly returns); the effect may be due to peroxide radical formation on the crystal surface (ATSDR, 1992).
Soil/Sediment: There is limited information on the behavior of antimony in soil and sediment. In aerobic surface soils, oxidation generally occurs. Methylated antimony compounds may be formed in waterlogged soil. Three organoantimony biotransformation products were found in a solution containing antimony trioxide (10 and 100 ppm) with nutrients and natural sediment from Puget Sound after 60 days of incubation under aerobic and anaerobic conditions; two of the products were identified – methylstibonic acid and dimethylstibonic acid. The rate and conditions affecting the transformation were not determined; it was estimated that <0.1% antimony in the incubate was transformed (ATSDR, 1992).

Physical-Chemical Properties

Physical State: Crystals, polymorphic [senarmontite = colorless cubic crystals; valentinite = white orthorhombic crystals]; exists in vapor phase (at 1500 °C) as Sb_4O_6 (HSDB, 2002; NRC, 2000)
Specific Gravity or Density Value: 5.2 g/cm^3 (senarmontite), 5.7 g/cm^3 (valentinite) (NRC, 2000)
Boiling Point (ºC): 1425 (HSDB, 2002); 1550 (NRC, 2000)
Melting Point (ºC): 655-656 (HSDB, 2002; NRC, 2000)
Vapor Pressure: 1 mm Hg at 574 °C (HSDB, 2002)
Solubility: Very-slightly soluble in cold water; slightly soluble in hot water, dilute sulfuric acid, and nitric acid; soluble in solutions of alkali hydroxide (e.g., potassium hydroxide) and sulfides, hydrochloric acid, tartaric acid, and acetic acid (HSDB, 2002; NRC, 2000)
Log P = Log K_{ow}: Not available
Bioconcentration Factor(s) (aquatic organisms): 0.5 to 390 (antimony); no bioconcentration observed in voles, rabbits, and small invertebrates (ATSDR, 1992).

B. Exposure Potential

U.S. Annual Production

1986: >1 - 10 million lb
1990: 10,000 - 500,000 lb
1994: >10 - 50 million lb
1998: >10 - 50 million lb
2002: >1 - 10 million lb
(U.S. EPA, 2005 [U.S. EPA IUR database; search by casno = 1309644])

Mining and Smelting

U.S. sources are mainly in Alaska, Idaho, Montana, and Nevada. Additional sources may occur in Mississippi Valley-type lead deposits in the Eastern United States.

1998: 500 metric tons from mine; 23,000 metric tons of primary antimony metal and oxides using foreign feedstocks; 7000 metric tons of secondary antimony (mostly in alloy form) was recovered at lead smelters (Carlin, 1999).

2004: No mine production or use of primary antimony in smelters was reported; 4100 metric tons of secondary antimony (mostly in alloy form) was recovered at lead smelters (Carlin, 2005).

Worldwide Annual Production

World resources are located in Bolivia, China, Mexico, Russia, and South Africa; annual production quantities were not given (Carlin, 2005).

Production Processes

Antimony trioxide is produced from the reaction of antimony trichloride ($SbCl_3$) with water, direct combination of metallic antimony with air or oxygen, roasting of antimony trisulfide, or alkaline hydrolysis of an antimony trihalide followed by dehydration of the hydrous oxide (HSDB, 2002; NRC, 2000).

Uses

Antimony trioxide is used in enamels as a paint pigment, glass, rubber, plastics, adhesives, textiles, and paper. It is used in flame proofing canvas, textiles, paper and plastics and in combination with some chlorinated or brominated flame retardants on commercial furniture, draperies, wall coverings and carpets (typically 2-10% by weight) (KEMI, 2005; NRC, 2000). It is commonly used with tetrabromobisphenol-A to enhance flame retardancy in printed circuit boards (HDP User Group International, Inc., 2005). The estimated distribution of uses is: flame retardants, 55%; transportation, including batteries, 18%; chemicals, 10%; ceramics and fiberglass, 7%; and other, 10% (Carlin, 2005; Environmental Defense, 2005; IARC, 1989; USCPSC, 2004).

Environmental Occurrence

Natural Occurrence: Antimony trioxide is the primary form of antimony in the atmosphere (IRIS, 2002). Antimony also occurs naturally as the ores of valentinite, senarmontite, exitelite, and weisspiessglanz. It is present in the earth's crusts at ~ 0.2-1 mg/kg and seawater has about $2x10^{-4}$ mg/kg. It is found mainly as a sulfide, oxide, or native metal, and at least 114 antimony-containing minerals are known (Environmental Defense, 2005; IPCS INTOX Databank, 2005).

Volatilization from Water/Soil: Under normal environmental conditions, antimony oxides in water are unlikely to volatilize due to their low concentration and the low concentration of their hydrolysis products as well as their strong polarity and extremely low vapor pressure (HSDB, 2002).

U.S. Environmental Releases: Significant amounts of antimony trioxide are released into the atmosphere during processing of antimony materials such as smelting of ores and combustion of fossil fuels which use high temperatures to volatilize the trioxide (HSDB, 2002). It is on the CERCLA List of Hazardous Substances; releases exceeding the Final Reportable Quantity of 1,000 lbs/454 kg are subject to reporting [40CFR 302.4 section IV.D.3.b] (HSDB, 2002). Most waste products from mining and smelting are discarded in large tailing piles, many of which are now abandoned. Acid conditions, often created in the tailing piles by the oxidation of pyrites, increase the potential for leaching (ATSDR, 1992). Nationwide on-site antimony releases reported in 2002

were land – 32 to 1,086,235 lbs/yr, water – 499 to 3,296 lbs/yr, and air – 1 to 10,644 lbs/yr (TOXMAP, 2005).

Environmental Fate: Most atmospheric releases of antimony substances result from high temperature industrial processes, the combustion of petroleum, petroleum products and coal, and the incineration of products that contain antimony. Antimony is oxidized at the high temperatures used in these processes resulting in the formation of antimony trioxide and possibly antimony tetraoxide and antimony pentoxide (HSDB, 2002).

Environmental Degradation: *Stibiobacter senarmontii*, an autotrophic bacterium isolated from antimony ore and grown in a mineral medium containing antimony trioxide, oxidized the trioxide at rates of 45.5-51.6 mg/month for senarmonite (cubic) and 13.5-19.3 mg/month for valentinite (rhombic). Limited antimony trioxide oxidation occurred in the sterile medium (HSDB, 2002).

Concentrations in Environmental Media

In 52 National Priorities List sites evaluated, the maximum antimony concentrations were 2100 ppb in groundwater, 1000 ppb in surface water, and 2550 ppm in soil (ATSDR, 1992).

Surface Waters: Mean antimony concentration in rainwater downwind from a copper smelter in Tacoma, WA, was 1.3 ppb; the concentration upwind was 0.03 ppb. Antimony content in snow particulate matter in samples from Montreal, Canada, ranged from 4 to 145 ppm; recent sampling of snow around Montreal found total concentrations of 1-8.7 ppb and enrichment factors of 39-590 (ATSDR, 1992).

Groundwater: Not available

Industrial Wastewater: Not available

Municipal Waste/Sewage: Not available

Ambient Air: High levels of antimony trioxide (>300 ppm) were detected downwind from a copper smelting plant (HSDB, 2002). Antimony concentrations in air particulates were the following (ATSDR, 1992):

- U.S. remote areas – 0.00045 to 1.19 ng/m^3
- U.S. rural areas – 0.6 to 7 ng/m^3
- U.S. urban areas – 0.5 to 171 ng/m^3
- Washington, DC (24-hour samples from 10 locations) – 1.1 to 1.0 ng/m^3
- New York state (geometric mean in aerosols from three rural/remote areas) – 1.0, 0.72, and 0.33 ng/m^3; the enrichment over crustal abundance ranged from 920-1,650. [Based on a mean of 1,880 in 29 cities, this indicates that the antimony is of anthropogenic origin.]
- North Atlantic – 0.086 ng/m^3
- North Pacific – 0.0037 ng/m^3
- Southern Norway – 0.54 ng/m^3 (air masses from the United Kingdom) and 0.07 ng/m^3 (air masses from over the Atlantic)
- Aerosols from "clean" continental and marine environments – 0.2 ng/m^3 in the Swiss Alps and 0.00045 ng.m^3 in American Samoa

Soils: Antimony concentration in soils throughout the continental United States – 0.48 ppm; range <1-8.8 ppm (Carlin, 2005)

- Sandstone – 0.05 ppm
- Igneous rock and limestone – 0.2 ppm
- Shales – 1.5 ppm
- Sludge-treated soils – 0.16 to 0.37 ppm (dry weight from 57 samples from agricultural area west of Toronto Ontario, Canada) (USCPSC, 2004).

Occupational Exposure

The major sources of exposure are from by-products of metal ore smelting (which may also contain arsenic), mining of antimony ore, and industries where antimony trioxide is used in the production of ceramic, glass, and alloys. Inhalation and dermal contact with dusts are the most common routes of exposures (IPCS INTOX Databank, 2005). Firemen and emergency workers may also be exposed to

antimony that is released when materials in which it is used as a fire retardant burn. It was found in soot and tracheal specimens at levels from 0.1 to 543 ppm (normal range is 0.1 to 124 ppm) from people who perished in fires. NIOSH estimated that 373,460 workers in the United States were potentially exposed to antimony (molecular formula unknown) from 1981-1983. More recent estimates indicate 226,645 workers were potentially exposed to antimony trioxide and other antimony compounds (ATSDR, 1992).

Exposure Limits (Standards and Criteria)

ACGIH TLV: 0.5 mg Sb/m^3 (8-hr time-weighted average [TWA])
NIOSH REL: 0.5 mg Sb/m^3 (10-hr TWA)
OSHA PEL: 0.5 mg Sb/m^3 (8-hr TWA)
EPA RfC: 0.2 µg Sb_2O_3/m^3

General Population Exposure

Foods, Beverages, Cosmetics, etc.

Food Tolerance Levels: Not available

Drinking Water Standards: The EPA Maximum Contaminant Level = 6 µg/L (Envirohealthaction, undated; HSDB, 2002)

Average Daily Intake: The average daily intake of antimony from food and water was estimated to be 100 µg/day (ATSDR, 1992).

Total Diet Estimates: The antimony concentration reported for a mixed diet was 9.3 ppb. This corresponds to 4.6 µg of antimony based on a 3,075 g diet/day (representative of the intake of a 25-30 year old U.S. male). The average antimony concentration in 12 table-ready foods (meats, vegetable, and seafood) ranged from 0.22-2.81 ppb. The antimony concentration in pooled human milk was 13 ppm (dry weight). Due to the low levels of antimony in water, the average dietary intake is estimated to be about 5 pg (ATSDR, 1992).

Cosmetics: A French study of the metallic content in soaps, shampoos, body oils, and cosmetics found that of all the products tested only lacquer contained 1.7 ppm antimony (ATSDR, 1992).

Other Exposure: Antimony (mean: 288 and 403 ppm) was found in certain composite resins used in British dental practices (ATSDR, 1992).

Ambient Environment

Environmental Exposure in the United States: The highest annual concentration of antimony in ambient air (452 ng/m^3) was measured in Laredo, Texas. Based on a standard inhalation rate of 20 m^3 of air/day, this would correspond to an average antimony intake of 9.0 µg/day. For cities with lower average antimony concentrations (Washington, DC, ~2 ng/m^3) antimony intake would only be 0.04 µg/day.

Levels in Tissues, Body Fluids, and Excreta: Autopsy data from unexposed Japanese adults showed the highest levels of antimony in skin (0.096 µg/g) and hair (0.096-0.12 µg/g). The mean body burden was 0.7 mg antimony. An estimated value of 7.9 mg for total body burden was reported by the International Commission on Radiological Protection (ICRP) for workers, who recommended reference values of 5.9 mg antimony in soft tissue and 2.0 mg in skeletal tissue (ATSDR, 1992). Urine samples from the U.S. population, six years and older, from the National Health and Nutrition Examination Survey (1999-2002) had mean concentrations of antimony that ranged from 0.130 µg/L for the 50th percentile to 0.380 µg/L for the 95th percentile; the geometric mean was 0.133 µg/L [0.1195, 0.373, and 0.125 µg/g of creatinine, respectively] (CDC, 2005). In workers from a smelter plant, antimony concentration ranged from trace amounts to 600 mg/L in urine. Concentrations of antimony in body fluids of women working in an antimony metallurgical plant were 10x those of controls in blood (concentration not given), 2.1-2.9 mg/100 mL in urine, ~3.3 mg/L in breast milk, 3.2-12.6 mg/100 mL in placental fluid, ~6.2 mg/100 mL in amniotic fluid, and ~6.3 mg/100 mL in umbilical cord (HSDB, 2002).

C. Toxicological Information

General Toxicity

In humans, lung is the primary target organ from inhalation exposure.

- Smelter plant workers heavily exposed to antimony trioxide developed gastritis, abdominal pain, diarrhea, vomiting; neuritis, dizziness, and headache (IPCS INTOX Databank, 2005).
- Exposure to dusts and fumes of antimony trioxide were also irritating to the respiratory tract and mucous membranes causing laryngitis, pharangitis, tracheitis, rhinitis, epistaxis, and bronchitis (IPCS INTOX Databank, 2005).
- Radiological evidence of pneumonitis was seen in six workers exposed for 2-12 hours to antimony smelter fumes (average antimony concentration was 10-12 mg/m^3; maximum concentration in the breathing zone was 70.7 mg/m^3). Inflammatory changes were characteristically perihilar with no evidence of peripheral parenchymal damage (IPCS INTOX Databank, 2005).
- Intoxication was also reported in medical use of antimony trioxide and potassium tartrate as tartar emetic in the treatment of a variety of conditions including malaise, fever, whooping cough, and syphilis. Three patients survived with no aftereffects, and one died from multiple organ failure after severe oral antimony intoxication as evidenced from the analysis of blood, urine, and tissue samples (Lauwers et al., 1990; PMID:2302961).
- Accidental intoxication from leaching of antimony from agate and ceramic containers into acidic beverages has been reported. Over 50 people required hospitalization after drinking lemonade contaminated with 13 mg antimony/L that had leached from an enamel container where drinks were stored overnight; subjects experienced burning sensation in the stomach, colic, nausea, vomiting and collapse but all recovered completely within several days (IPCS INTOX Databank, 2005).

Dermal/Ocular Exposure

Human Studies

- Antimony trioxide is an irritant that typically causes antimony dermatitis during chronic occupational exposure. Lesions arise on the arms, legs and in the flexures, but not the face, hands, or feet. Papules and pustules are primarily seen around sweat and sebaceous glands with areas of eczema and lichenification occurring mainly in the summer (IPCS INTOX Databank, 2005).
- Male employees (n=23), primarily furnace workers, at an antimony trioxide production plant developed skin lesions within 2 weeks of exposure. Itching, erythmatous papules, and pustular eruptions were characteristic, usually on dust laden sweaty areas of the skin. Lesions resolved over 2 weeks in individuals removed to cooler parts of the factory. Histological examination showed epidermal cellular necrosis associated with an acute dermal inflammatory reaction (IPCS INTOX Databank, 2005).
- Conjunctivitis was also reported in 14/51 workers exposed to antimony trioxide dusts in a smelter plant (IPCS INTOX Databank, 2005).

Animal Studies

- No skin effects were noted in rabbits treated with 21 g of antimony trioxide in an aqueous methylcellulose paste for one week. Mild irritation was noted 72 hours after 420 mg was applied to the pre-moistened skin of rabbits for 24 hours. Death was reported in rabbits after a single dermal application of 6.7 g/kg in corn oil.
- Administration of 50% suspension of antimony in mineral oil did not cause irritation to rabbit skin or eyes.
- Instillation of a dry antimony powder did not cause corneal injury in rabbit eyes (Union Carbide, 1978).

- Rats developed corneal irregularities after whole body inhalation exposure to antimony trioxide (0.21-19.6 mg/m3) for 6 hr/day, 5 days/week for two weeks (USCPSC, 2004).

Cardiovascular and Peripheral Vascular Toxicity

Human Studies

[cited in IPCS INTOX Databank (2005) unless otherwise indicated]

- Changes in electrocardiograms (ECG) have been reported in patients treated with antimony-containing drugs.
- Cardiac complaints and changes in ECGs were reported in 14 workers occupationally exposed to antimony trioxide dust (significant antimony trisulphide exposure also occurred).
- No excess deaths from ischemic heart disease were seen in workers exposed to antimony trioxide in a processing plant compared to controls at the same site.
- Two patients presented moderate bradyrhythmic dysfunctions following acute antimony ingestion and phlebitis occurred in patients accidentally ingesting antimony potassium tartrate.
- A mortality study of 1,014 men (928 of Spanish ancestry) employed in a Texas antimony smelter between 1937 and 1971 showed some increased mortality from lung cancer and nonmalignant respiratory disease. Using ethnic-specific lung cancer death rates in Texas for comparison, mortality from lung-cancer among antimony workers was elevated [standardized mortality ratio (SMR) 1.39, 90% CI 1.01-1.88] and a significant positive trend in mortality with increasing duration of employment was seen. When ischemic heart disease death rates from three different Spanish-surname populations were used for comparison, the rate ratios for ischemic heart disease were 0.91 (90% CI 0.84-1.09), 1.22 (90% CI 0.78-1.8) and 1.49 (90% CI 0.84-2.63) suggesting that nonmalignant respiratory heart disease may contribute to increased mortality in workers exposed to antimony but conclusions are limited by possible confounders and the difficulty in identifying appropriate referent groups (Schnorr et al., 1995; PMID:7611310).
- Altered ECG readings were reported in individuals exposed to repeated injections of antimony compounds (e.g., sodium antimonylgluconate, sodium antimony tartrate) for therapeutic treatment of a parasitic disease. Some readings did not return to normal until 6 weeks after the last injection. Pentavalent antimony appears to be less cardiotoxic than trivalent; ECG readings were affected after 4 days of treatment with trivalent antimony (0.98 mg/kg/day) and after 3 weeks of treatment with pentavalent antimony (7.2 mg/kg/day) (ATSDR, 1992).

Animal Studies: Altered ECG readings as well as decreased blood pressure, increased heart rate, and decreased contractile force were observed in animals following trivalent antimony injection (ATSDR, 1992).

Chemical Disposition, Metabolism, and Toxicokinetics

Human Studies

Absorption: Antimony trioxide is absorbed following inhalation exposure; elevated blood and urine antimony levels were found in workers occupationally exposed to antimony (NRC, 2000). Gastrointestinal absorption of antimony trioxide is poor in man (IPCS INTOX Databank, 2005).

Distribution: Increased antimony concentrations were found in the lungs of workers occupationally exposed to antimony via inhalation (NRC, 2000). Antimony concentrations in liver and kidney tissue was not significantly different in workers compared to controls, suggesting that inhaled antimony may be retained in the lungs for several years without significant systemic distribution (IPCS INTOX Databank, 2005).

Metabolism and Excretion: Antimony compounds are eliminated mainly in the urine, with small amounts appearing in feces via bile after conjugation with glutathione. A significant amount of antimony excreted in bile undergoes enterohepatic circulation. A renal elimination half-life of 4 days following inhalation of antimony trioxide was estimated in 21 employees of a starter battery manufacturing plant. Antimony concentrations measured in urine (range 5.8-145.3 µg/L) from patients collected 6-24 months after antimony therapy were high compared to untreated controls

(range 2.9-9.1 µg/L) (IPCS INTOX Databank, 2005). Elevated levels were also measured in lung tissue of post-mortem and ~20-year retired workers, indicating a long half-life for lung clearance. Inhaled antimony is retained in the lung but is relatively rapidly cleared from other tissues; clearance and retention depend mainly on solubility (IRIS, 2002; NRC, 2000).

Animal Studies

Absorption: In rabbits, antimony trioxide is absorbed dermally (NRC, 2000).

Distribution: After chronic oral administration of antimony trioxide (2% in diet for 8 months) to rats, high antimony concentrations were detected in the thyroid and GI contents, as well as in the spleen, kidney, heart, bone, muscle, lungs, liver, and GI tissue (NRC, 2000).

- The highest antimony concentrations in rat tissues after receiving 1% antimony trioxide in the diet for 12 weeks were in the following order: blood, spleen, lungs, kidneys, hair, liver, and heart.
- No particular difference in tissue distribution in rats compared to rabbits was observed with the 2% diet; mean antimony levels ranged from 6.7-88 µg/g (HSDB, 2002).
- High antimony concentrations were found in the lungs and liver and lower levels in the kidney, stomach, and trachea of Syrian golden hamsters following intratracheal instillation of 1.52 mg/kg bw antimony trioxide (NRC, 2000).

Metabolism and Excretion: The majority of the urinary excretion of antimony by rats exposed via inhalation to antimony trioxide (119 mg dust/m^3 for 80 hr) occurred within the first 3 days.

- After oral administration of a single dose (200 mg) 3% of the dose was recovered in the urine within 8 days.
- Following chronic oral administration of antimony trioxide (2% in the diet for 8 months), ~99% of fecal excretion and most of urinary excretion of antimony occurred within 7 days after treatment was stopped.
- After intratracheal instillation of antimony trioxide (1.52 mg/kg bw) in Syrian golden hamsters, 20% of the dose was cleared from lungs in the first 20 hours. A two-phase clearance was suggested with biological half-lives of approximately 40 hours for the initial phase and 20-40 days for the second phase (HSDB, 2002; USPCS, 2004).

Subchronic Exposures

Subchronic oral administration of antimony trioxide (420-490 mg/kg/day) in rats produced hepatic cord swelling, decreased red blood cell counts, loss in weight gain, and minor changes in relative or absolute organ weights. A LOAEL of 420 mg/kg/day was reported for Wistar rats fed antimony trioxide in the diet for 24 weeks based on mild liver toxicity and decreased red blood cell counts (USCPSC, 2004).

Route:	oral (feed)
Species:	rat (strain and sex not given)
Dose/Duration:	670 mg/kg/day for 12 wk
Observation Time:	not provided
Effects:	decreased weight gain, spleen weight, and heart weight; increased lung weight
Source(s):	Hiraoka (1986; cited by NRC, 2000)

Route:	oral (feed)
Species:	rat, Wistar, males
Dose/Duration:	500 or 1000 mg/kg/day for 24 wk
Observation Time:	not provided
Effects:	decreased red blood cell count; increased serum glutamic oxaloacetic transaminase [LOAEL=500 mg/kg/day]
Source(s):	Sunagawa (1981; cited by NRC, 2000)

Route:	oral (feed)
Species:	rat, Wistar, males and females
Dose/Duration:	84-1879 mg/kg/day for 90 days
Observation Time:	not provided
Effects:	In high-dose males: increased triglycerides, red blood cell count, and urine volume; decreased alkaline phosphatase activity In high-dose females: increased red blood cell count, urine volume, serum cholesterol, and aspartate and alanine aminotransferase; decreased alkaline phosphatase activity (mid-dose too) and urine specific gravity [NOEAL=494 mg/kg/day; LOEAL=1879 mg/kg/day]
Source(s):	Hext et al. (1999; cited by NRC, 2000)

Chronic Exposures

Human Studies: Chronic occupational exposure may cause "antimony pneumoconiosis." Radiological findings included diffuse, dense, punctate, non-confluent opacities, predominantly in the middle and lower lung fields, sometimes associated with pleural adhesions. These changes developed after at least 10 years of exposure to dusts containing 90% antimony trioxide with some antimony pentoxide and small amounts (up to 5%) of silica. Cough (31/51 subjects) and exertional breathlessness (26 cases) as well as wheezing, chest pain or generalized weakness were reported. Nine workers had obstructive lung function defects with a combined restrictive/obstructive picture in five cases but no isolated restrictive defects or radiological evidence of diffuse fibrosis (IPCS INTOX Databank, 2005).

Animal Studies: Pneumonitis was observed in rats and rabbits exposed to antimony trioxide (90-125 mg/m^3 for 100 hr/month for up to 14 months). In addition, lipoid pneumonia, fibrous thickening of alveolar walls, and focal fibrosis were seen. Rabbits were more susceptible than rats (HSDB, 2002).

Route:	inhalation
Species:	rat, Fischer 344, males and females
Dose:	0.06, 0.51, or 4.5 mg/m^3
Duration:	6 hr/day, 5 days/wk for 1 yr
Observation Time:	1 yr
Effects:	increased alveolar macrophage [LOAEL=0.06 mg/m^3]; interstitial inflammation and granulomatous inflammation [NOAEL=0.51 mg/m^3 and LOAEL=4.5 mg/m^3]
Source(s):	Newton et al. (1994 [PMID:8056203]; cited by NRC, 2000)

Route:	inhalation
Species:	rat, Fischer 344, males and females
Dose:	0.25, 1.08, 4.92, or 23.46 mg/m^3
Duration:	6 hr/day, 5 days/wk for 13 wk
Observation Time:	27 wk
Effects:	6% decreased body weight [NOAEL=4.92 mg/m^3 and LOAEL=23.46 mg/m^3 (M)]; increased lung weight [NOAEL=1.08 mg/m^3 and LOAEL=4.92 mg/m^3 (M)]; chronic interstitial inflammation, granulomatous inflammation, and increased alveolar macrophages [NOAEL=1.08 mg/m^3 (F), 4.92 mg/m^3 (M) and LOAEL=4.92 mg/m^3 (F), 23.46 mg/m^3 (M)]
Source(s):	Newton et al. (1994 [PMID:8056203]; cited by NRC, 2000)

Route:	inhalation
Species:	rat, CDF Fischer, females
Dose:	1.9 or 5.0 mg/m^3
Duration:	6 hr/day, 5 days/wk for 1 yr
Observation Time:	not provided
Effects:	increased blood urea nitrogen at high concentration, which was statistically significant after 6 months exposure; discoloration and increased alveolar macrophages [LOAEL=1.9 mg/m^3]; interstitial inflammation and granulomatous inflammation [NOAEL=5.0 mg/m^3 and LOAEL=1.9 mg/m^3]
Source(s):	Watt (1983 diss.; cited by NRC, 2000)

Route:	inhalation
Species:	rat, Wistar, males and females
Dose:	45.5 mg/m^3
Duration:	7 hr/day, 5 days/wk for 1 yr
Observation Time:	20 wk
Effects:	38,300 µg Sb/g in lungs of males versus 25,000 µg Sb/g in those of females; interstitial fibrosis, alveolar-wall cell hypertrophy and hyperplasia, and cuboidal and columnar cell metaplasia of the lungs; effects were more pronounced in females [LOAEL=45.5 mg/m^3]
Source(s):	Groth et al. (1986; cited by NRC, 2000); HSDB (2002)

Route:	inhalation
Species:	rat
Dose:	100-125 mg/m^3
Duration:	100 hr/month for 14.5 months
Observation Time:	not provided
Effects:	diffuse, interstitial fibrosis; 18% died of pneumonia [LOAEL=100 mg/m^3]
Source(s):	Gross et al. (1955; cited by NRC, 2000)

Route:	inhalation
Species:	rabbit
Dose:	89 mg/m^3
Duration:	100 hr/month for 10 months
Observation Time:	not provided
Effects:	85% died of pneumonia [LOAEL=89 mg/m^3]
Source(s):	Gross et al. (1955; cited by NRC, 2000)

Route:	inhalation
Species:	guinea pig
Dose:	45.4 mg/m^3 (average)
Duration:	2-3 hr/day, 7 days/wk for 6 months
Observation Time:	not provided
Effects:	pneumonitis, liver and spleen effects, decreased white blood cell counts [LOAEL=45.4 mg/m^3]
Source(s):	Dernehl et al. (1945; cited by NRC, 2000)
Note:	No cardiac lesions were seen in the electrocardiogram (HSDB, 2000).

Reproductive and Developmental Toxicity

Human Studies: Women working in an antimony plant had increased incidence of unspecified gynecological problems, early interruption of pregnancy, and spontaneous late abortions (NRC, 2000). The incidence of spontaneous abortions was 12.5% (versus 4.1% in controls); the incidence of premature births was 3.4% (versus 1.2% in controls). Body weight of the children started to significantly lag after one year (IRIS, 2002).

Animal Studies

- Rats exposed to antimony trioxide (0.027, 0.082, or 0.27 mg/m^3 for 24 hours/day) for 21 days of gestation showed increased pre- and post-implantation embryo deaths at the high dose, and pre-implantation loss and fetal growth retardation at the mid dose. The NOAEL was 0.027 mg/m^3 and the LOAEL was 0.082 mg/m^3. Antimony trioxide (250 mg/m^3, 4hr/day for two months) also decreased the number of offspring and disrupted ovulation in rats (Grin et al., 1987; cited by NRC, 2000; HSDB, 2002).
- Maternal effects were observed in rats exposed to antimony trioxide via nose-only inhalation (1.5, 3.0, or 6.0 mg/m^3 [actual concentrations of 2.6, 4.4, or 6.3 mg/m^3] for 6 hours/day from days 0-19 of gestation); lung weights were 24, 31, and 39% greater than controls for the low, mid, and high doses, respectively. Diffuse accumulation of pigmented alveolar macrophages and accumulation of antimony trioxide particulate matter were seen. The LOAEL for maternal effects was 2.6 mg/m^3. The NOEL for developmental toxicity was 6.3 mg/m^3 (Serex, 2004 lett.).
- Pregnancy occurred in 16 of 24 rats exposed to antimony trioxide (250 mg/m^3, 4 hrs/day for 1.5-2 months) that were mated and then treatment continued until 3-5 days before expected delivery compared to 10 of 10 pregnancies observed in controls. No effect on offspring weights at birth or weaning was observed (HSDB, 2002). Average litter size was 6.2 compared to 8.3 in controls. No teratogenic effects were observed (IRIS, 2002).
- No treatment-related effects were seen on the weight of testis, epididymis, ventral prostate, or seminal vesicles; on sperm count, sperm motility, or sperm morphology; or on histopathology of the testis in Wistar rats or CD-1 mice treated with antimony trioxide (1,000 mg/kg suspended in water) for 3 or 5 days/week, respectively, for 4 weeks (USCPSC, 2004).

Carcinogenicity

Human Studies: The IARC overall evaluation for antimony trioxide was "probably carcinogenic to humans" (Group 2B). There was inadequate evidence in humans and sufficient evidence for carcinogenicity in experimental animals (HSDB, 2002; IARC, 1989; NRC, 2000). [Note: Assessment was made prior to publication of the negative study in Fischer 344 rats cited in NRC (2000).]

Animal Studies

- Inhalation studies in Fischer 344 rats (0.06, 0.51, or 4.5 mg/m^3 for 6 hr/day, 5 days/week for 1 year) did not increase tumor incidence (Newton et al., 1994 [PMID:8056203]; cited by NRC, 2000).
- Inhalation studies in Wistar rats (50 mg/m^3 for 7 hr/day, 5 days/week for 1 year) reported increased incidence of lung tumors in females only (19 of 70 compared to 0 of 70 controls): 9 squamous-cell carcinomas, 5 scirrhous carcinomas, and 11 bronchiolalveolar adenomas and carcinomas (Groth et al., 1986; cited by NRC, 2000).
- Inhalation studies of commercial grade antimony trioxide in female Fischer CDF rats (1.6 or 4.2 mg/m^3 for 6 hr/day, 5 days/week for 13 months) induced lung tumors that were localized in the bronchioloalveolar region of 14/18 high-dose rats (3 adenomas, 9 scirrhous carcinomas, 2 squamous-cell carcinomas) 12 months after the last treatment. One bronchioalveolar adenoma was observed in a single low-dose rat. Scirrhous carcinomas were also seen in high-dose rats that died or were killed prior to terminal sacrifice (Watt, 1983 diss.; cited by IARC, 1989).

Genetic Toxicity

Microbial Gene Mutation

- Not mutagenic in *Salmonella typhimurium* or *Escherichia coli* strains (NRC, 2000)
- DNA damage in *Bacillus subtilis* (NRC, 2000)

Human Studies (*in vitro* and *in vivo*)

- No induction of sister chromatid exchange or micronuclei in workers involved with applying antimony trioxide to fabric compared to control group (USCPSC, 2004)
- A significantly higher proportion of exposed workers with oxidative DNA damage (the formamido pyrimidine glycosylase-modified comet assay) [Note: confounding factors or exposure to other chemicals cannot be ruled out as a cause] (USCPSC, 2004)
- No clastogenic response in isolated human peripheral lymphocytes (USCPSC, 2004)

Animal Studies (*in vitro* and *in vivo*)

Gene Mutation

- No unscheduled DNA synthesis in rat liver via oral gavage (up to 4,200 mg/kg) (USCPSC, 2004)

Cytogenetic Effects

- Increased incidence of sister chromatid exchange in Chinese hamster V79 cells (NRC, 2000)
- Chromosome aberrations induced in mouse bone marrow from repeated oral administration of antimony trioxide [400, 667, or 1000 mg/kg for 21 days]. A single dose was negative (NRC, 2000).
- No increase in micronucleated polychromatic erythrocytes in mouse bone marrow cells *in vivo* (NRC, 2000)

Germ Cell Effects: Not available

Neurotoxicity

Human Studies: One smelter worker exposed to high levels of antimony oxide in air (10 mg/m^3) reported nerve tenderness and tingling; the worker was also exposed to several other chemicals (USCPSC, 2004). In an antimony smelting plant, neuritis, dizziness, and headache were reported in workers exposed to antimony trioxide fumes (IPCS INTOX Databank, 2005).

Animal Studies: Abnormal gait was noted in one rabbit after dermal exposure to 6.7 g/kg in corn oil for 24 hours (USCPSC, 2004).

Immunotoxicity

Human Studies: Antimony trioxide was not a sensitizer or a skin irritant in 52 subjects that received 9 dermal applications (dose not provided) over a 3-week period followed with a single dose two weeks later (NRC, 2000).

Animal Studies: In guinea pigs, 9 dermal applications of antimony trioxide (31 or 49 mg/kg) in a fat/acetone/dioxane mixture or 4 intradermal injections of antimony trioxide (1 mg) in acetone-dimethyl phthalate or propylene glycol solution for 3 weeks, followed two weeks later by challenge applications, produced no sensitization (NRC, 2000).

D. Mechanistic Data

The mechanism of toxicity of antimony compounds is unclear but may involve disruption of thiol proteins via binding to sulphydryl groups (IPCS INTOX Databank, 2005).

Target Organs/Tissues

Human: Lungs

Animal: Lungs

Modes of Action

Human: Not available

Animal: Not available

Effects on Metabolic Pathways: Not available

Structure Activity Relationships

Antimony Trisulfide [Sb_2S_3, CAS RN 1345-04-6]: The toxic effect associated with exposure to antimony trioxide is cardiotoxicity (IRIS, 2002). It is "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate and limited evidence for carcinogenicity in humans and experimental animals, respectively (IARC, 1989).

Human Data: Abrasives industry workers (n=124) exposed to antimony trisulfide (0.6-5.5 mg/m^3) for 8-24 months reported increased mortality and morbidity from heart disease. Six workers died suddenly and others died of chronic disease. ECG changes were seen in 37/75 workers. After antimony trisulfied was discontinued, no new deaths due to heart disease and no abnormal increase in heart/circulatory problems were reported, although ECG changes persisted in 12 workers (TRI, Inc., 2002).

Animal Data: Wistar rats exposed by nose-only inhalation to 5,000 mg/m^3 Sb_2S_3 (3,600 mg/m^3 Sb) for 4 hours developed black foci in the lungs; deaths or other treatment-related effects did not occur over a 15-day period. A dose of 2,000 mg/kg Sb_2S_3 (1,440 mg/m^3 Sb) administered by gavage or applied to intact skin for 24 hours under occlusion caused no deaths or signs of toxicity in rats during a 15-day period (TRI, Inc., 2002). Antimony ore concentrate (mainly Sb_2S_3) tested in rats by inhalation exposure produced a significant increase in the incidence of lung tumors (scirrhous and squamous-cell carcinomas and bronchioloalveolar tumors) in females only (HSDB, 2002; NRC, 2000).

References

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological profile for antimony and compounds. ATSDR, U.S. Public Health Service, Atlanta, GA, 148 pp. Internet address: http://www.atsdr.cdc.gov/toxprofiles/tp23.pdf.

Carlin, J.F., Jr. 1999. Antimony. U.S. Geological Survey, Mineral Commodity Summaries, January 1999, pp. 24-25.

Carlin, J.F., Jr. 2005. Antimony. U.S. Geological Survey, Mineral Commodity Summaries, January 2005, pp. 22-23.

CDC (Centers for Disease Control and Prevention). 2005. Third National Report on Human Exposure to Environmental Chemicals. National Center for Environmental Health, Division of Laboratory Sciences, Atlanta, GA. NCEH Pub. No. 05-0570. Internet address: http://www.cdc.gov/exposurereport/3rd/pdf/thirdreport.pdf.

Dernehl, C.U., Nau, C.A. and Sweets, H.H. 1945. Animal studies on the toxicity of inhaled antimony trioxide. J Ind Hyg Toxicol, 27(9):256-262. Cited by NRC (2000).

Envirohealthaction. Undated. Heavy Metals. Internet address: http://www.envirohealthaction.org/upload_files/Heavy_Metals.pdf.

Environmental Defense. 2005. Antimony compounds. Internet address: http://www.scorecard.org/chemical-profiles/html/antimony.html. Last accessed on March 16, 2005.

Grin, N.V., Govorunova, N.N., Bessemrnyi, A.N., and Pavlovich, L.V. 1987. Embryotoxic action of antimony oxide in an experiment [Russian]. Gig Sanit, 10:85-86. Cited by NRC (2000).

Gross, P., Westrick M.L., Brown, J.H.U., Srsic, R.P., Schrenk, H.H., and Hatch, T.F. 1955. Toxicologic study of calcium halophosphate phosphors and antimony trioxide. II. Pulmonary studies. Arch Ind Health, 11:479–486. Cited by NRC (2000).

Groth, D.H., Stettler, L.E., Burg, J.R., Busey, W.M., Grant, G.C., and Wong, L. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J Toxicol Environ Health, 18(4):607-626. Cited by NRC (2000).

HDP (High Density Packaging) User Group International, Inc. 2005. Environmental assessment of halogen-free printed circuit boards. Internet address: http://www.hdpug.org/public/4-papers/2004/dfe/dfe-phase-2.pdf.

Hext, P.M., Pinto, P.J., and Rimmel, B.A. 1999. Subchronic feeding study of antimony trioxide in rats. J Appl Toxicol, 19(3):205-209. Cited by NRC (2000).

Hiraoka, N. 1986. The toxicity and organ distribution of antimony after chronic administration to rats. J Kyoto Prefect Univ Med, 95:997-1017. Cited by NRC (2000).

HSDB (Hazardous Substances Data Bank) 2002. Antimony trioxide. HSDB No. 436. Profile last updated on November 8, 2002. Search at main Internet address: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. Last accessed on March 29, 2005.

IARC (International Agency for Research on Cancer). 1989. Antimony trioxide and antimony trisulfide. Internet address: http://www.inchem.org/documents/iarc/vol47/47-11.html. Last updated on January 21, 1998. Last accessed on March 16, 2005.

IPCS INTOX (International Programme of Chemical Safety) Databank 2005. Antimony Trioxide. UKPID Monograph. Internet address: http://www.intox.org/databank/documents/chemical/antxide/ukpid38.htm. Last accessed on March 16, 2005.

IRIS (Integrated Risk Information System). 2002. Antimony trioxide (CASRN 1309-64-4). IRIS Record No. 0676. Database provided by the U.S. Environmental Protection Agency. Profile last updated on December 3, 2002. Internet address: http://www.epa.gov/iris/subst/0676.htm. (Online file) last updated on November 18, 2004. Last accessed on April 7, 2005.

KEMI. 2005. Information on substances: Antimony trioxide. Internet address: http://www.kemi.se/kemamne_eng/antimon_eng.htm. Last accessed on March 16, 2005. Available now at Internet address: http://apps.kemi.se/flodessok/floden/kemamne_eng/antimon_eng.htm. Last accessed on March 21, 2006.

Lauwers, L.F., Roelants, A., Rosseel, P.M., Heyndrickx, B., and Baute, L. 1990. Oral antimony intoxication in man. Crit Care Med, 18(3):324-326. Abstract from PubMed 2302961.

Newton, P.E., Bolte, H.F., Daly, I.W., Pillsbury, B.D., Terrill, J.B., Drew, R.T., Ben-Dyke, R., Sheldon, A.W., and Rubin, L.F. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol, 22(4):561-576. Abstract from PubMed 8056203. Also cited by NRC (2000).

NRC (National Research Council). 2000. Toxicological Risks of Selected Flame-Retardant Chemicals. National Academy Press, Washington, DC. Internet address: http://www.nap.edu/openbook/0309070473/html/R1.html.

Schnorr, T.M., Steenland, K., Thus, M.J., and Rinsky, R.A. 1995. Mortality in a cohort of antimony smelter workers. Am J Ind Med, 27(5):759-770.

Serex, T.L. 2004 lett. Letter to the Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency, regarding TSCA Section 8(e) Notification of Antimony Trioxide (CAS No. 1309-64-4), from T.L. Serex, Lead Technical Advisor to the International Antimony Oxide Industry Association (IAOIA). Internet address: http://www.epa.gov/oppt/tsca8e/pubs/8ehq/2004/march04/8ehq-0204-15523a.pdf.

Sunagawa, S. 1981. Experimental studies on antimony poisoning [Japanese]. Igaku Kenkyu, 51(3): 129-142. Cited by NRC (2000).

TOXMAP. 2005. Releases map: Antimony (7440-36-0). TRI-2002 – 63 on-site releases reported nationwide. Internet address: http://toxmap.nlm.nih.gov/toxmap/releases/identifyAll.do. Last accessed on March 31, 2005.

TRI (Technical Resources, International), Inc. 2002. Summary of data for chemical selection: Antimony trisulfide. Prepared for NCI to support nomination under contract no. N0-CB-07007 (CSWG: 4/02; NTP: 9/02). Available at http://ntp.niehs.nih.gov/ntp/htdocs/Chem_Background/ExSumPdf/antimony_trisulfide.pdf.

Union Carbide Corporation. 1978. Antimony trioxide range-finding toxicity studies. Document Number 878210813. Microfiche No. 206062. Union Carbide Corp., Corporation of Health Safety and Environmental Affair Department, Danbury, CT.

USCPSC (United States Consumer Product Safety Commission). 2004. Qualitative assessment of potential risk from the use of flame retardant chemicals in mattresses. Memorandum to M. Neily, Director, Division of Combustion and Fire Sciences, Directorate for Engineering Sciences from T.A. Thomas and P. Brundage, both of the Division of Health Sciences, October 25, 2004.

U.S. EPA (Environmental Protection Agency). 2005. Inventory Update Rule. [Search by casno 1309644.] Office of Pollution, Prevention and Toxics, U.S. EPA. Internet address: http://www.epa.gov/opptintr/iur/iur02/search03.htm. Last updated on March 29, 2005. Last accessed on March 29, 2005.

Watt, W.D. 1983 diss. Chronic Inhalation Toxicity of Antimony Trioxide: Validation of the Threshold Limit Value. Dissertation, Wayne State University, Detroit, MI. Cited by IARC (1989) and NRC (2000).