SUMMARY OF DATA FOR CHEMICAL SELECTION

Antimony Trisulfide
1345-04-6

BASIS OF NOMINATION TO THE NTP

Antimony trisulfide is brought to the attention of the Chemical Selection Working Group as a widely used chemical with insufficient information available to assess its carcinogenic potential.

This chemical came to the attention of the National Cancer Institute (NCI) from a review of chemicals viewed as "not classifiable" as to carcinogenicity to humans (Group 3) by the International Agency for Research on Cancer (IARC). IARC noted the limited evidence of carcinogenicity for antimony trisulfide, primarily from an inhalation study in which rats were exposed to antimony ore concentrate for one year and then held for up to 20 weeks post-exposure. In this study, interstitial fibrosis and alveolar-cell hyperplasia and metaplasia were observed in both males and females and lung tumors were observed in the females. This limited study has been challenged in various reviews because of impurities in the test material, including small amounts of arsenic.

Exposure to antimony trisulfide in its various forms, including grey antimony, antimony orange, and orange concentrate appears to be moderately high. The National Institute for Occupational Safety and Health (NIOSH) estimates that approximately 27 thousand workers in 34 industries are potentially exposed to antimony trisulfide based on information collected in the 1980s. This compound has a variety of uses, including non-asbestos friction material for brake and clutch linings, fireworks and other pyrotechnics, camouflage paints, pigments in ruby glass, and photoconductors. Crude antimony sulfide is obtained from mining operations.

SELECTION STATUS
ACTION BY CSWG: June 20, 2002

Studies requested: Carcinogenicity

Priority: Moderately High

Rationale/Remarks:
Significant human exposure to various forms of antimony trisulfide

The National Institute for Occupational Safety and Health.(NIOSH) recently nominated antimony trisulfide for listing in the Report on Carcinogens as a substance reasonably anticipated to be a human carcinogen. Such a listing would address the CSWG's concerns regarding this chemical.

INPUT FORM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Director of the TSCA Interagency Testing Committee, provided a copy of the Environmental Protection Agency (EPA) Negotiated Testing Agreement (NTA) and Final Acceptance Notice (FAN) for antimony compounds. Information on antimony trisulfide contained in these 1983 documents has been incorporated into this revised Summary Sheet as appropriate.

At the CSWG meeting, Dr. Mark Toraason indicated that NIOSH had requested inclusion of antimony trioxide and antimony trisulfide in the Report on Carcinogens on January 9, 2002. After the CSWG meeting, Dr. Toraason forwarded a copy of NIOSH's supporting documentation, "Nomination of Antimony Trioxide and Antimony Trisulfide to be Reviewed for Listing in the NTP's Report on Carcinogens (ROC)".[1] NIOSH conclusions regarding antimony trisulfide rely heavily on the inhalation study in rats (see Groth *et al*., 1986) and on several human mortality studies also showing lung cancer following antimony exposure. Summaries of the antimony trisulfide studies cited by NIOSH were available to the CSWG during the group's deliberation in June.

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[1] NIOSH was unable to obtain a copy of the dissertation by Watt involving the exposure of rats to antimony trioxide. Dr. Walker commented at the CSWG meeting that the ITC questioned Dr. Watt extensively; this information and a copy of Dr. Watt's dissertation are available in the EPA docket prepared to support the ITC decision on antimony compounds (OPTS-42021).

CHEMICAL IDENTIFICATION

CAS Registry No.:	1345-04-6

Synonyms: Antimonous sulfide; grey antimony; antimony
orange; antimony sesquisulfide; antimony sulfide;
antimony trisulfide colloid; antimony vermilion;
antimony(III)sulfide;   antimony(3+) sulfide; CI
77060; CI Pigment Red 107; crimson antimony;
diantimony trisulfide; Lymphoscan; needle
antimony (ChemID, 2002; Herbst *et al.*, 1985)

Structure, Molecular Formula, and Molecular Weight:
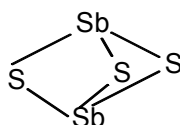
S_3Sb_2 Mol. wt: 339.72

Structural Class: Inorganic

Chemical and Physical Properties: Antimony belongs to Group VB of the Periodic
Table. It is correctly classified as a metalloid,
although it is often referred to as a metal.

Description: Antimony trisulfide exists as a black crystalline
solid and an amorphous red-orange powder; the
mixture can be carmine or brownish red (Freedman
et al., 1992; Herbst *et al.*, 1985).

In its mineral form, stibnite [Cas No. 1317-86-8],
antimony trisulfide has an orthorhombic-
bipyramidal crystalline structure, sometimes very
large and solid and at other times slender and
fragile (IARC, 1989)

Melting Point: 550 °C (Merck, 2001)

Solubility: Very slightly soluble in water (0.000175g/100cc @
18 °C; soluble in alkalies and in concentrated
hydrochloric acid and sulfide solutions, and in
ethanol (Herbst *et al.*, 1985; Lewis, 2002; Lide,
2001; Merck, 2001)

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Density/Specific Gravity: 4.562 g/cm3 (Lide, 2001)

Reactivity: Flammable/combustible material; may be ignited by friction, heat, sparks, or flames (HSDB, 2002)

Technical Products and Impurities: Antimony (III) sulfide, 68.5% Sb, 27% sulfur, as a black powder, is available from Sigma-Aldrich (2001a,b).

If antimony ore contains more than 90% stibnite, it can be sold directly for producing antimony compounds or conversion to antimony metal (Herbst *et al.*, 1985). Crude materials marketed for the manufacturing of pure antimony products (mostly oxide) consist of antimony sulfide concentrate and lump antimony sulfide ore (USGS, 2001).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Processes: Amorphous (red to yellow-orange) antimony trisulfide can be prepared by treating an antimony trichloride solution with hydrogen sulfide or sodium thiosulfate, or by heating metallic antimony or antimony trioxide with sulfur (Freedman *et al.*, 1992).

Stibnite has a low melting point, and it can be extracted by melting if the ore contains 45-60% antimony and is free of lead and arsenic. This technique is called liquation. Sulfide ores with antimony contents between 5 and 25% are roasted to give volatile Sb_2O_3 which is reduced directly to the metal. Low-grade and complex ores or ores in which minerals are finely dispersed are beneficiated by flotation (Herbst *et al.*, 1985).

Production/Import Level:

Although industrial consumption of antimony in 2000 was 16,700 metric tons, only 100 metric tons consisted of antimony sulfide ores and the crude concentrates. The sole domestic antimony producer in the United States in 2000, Sunshine Mining Company, recovered antimony concentrates as a byproduct of the treatment of complex silver-copper-antimony sulfide ore (Carlin, 2000; USGS, 2002).

In 2000, imports of antimony ore and concentrate (antimony sulfides) totaled 3,690 metric tons based on antimony content. The primary exporters were Australia (1,150 metric tons), China (1,000 metric tons), and Mexico (903 metric tons) (Carlin, 2000).

To determine the exact amount of pure antimony trisulfide consumed from statistics on antimony produced by the US Geological Survey (USGS) is difficult because the USGS does not provide chemical-specific breakdowns for antimony compounds. The greatest use of antimony, as a flame retardant, accounted for 9,930 metric tons of antimony, primarily as antimony oxide. Of the 4,110 metric tons of nonmetal antimony consumed in 2000, 862 metric tons was used in ceramics and glass, 1,960 metric tons was used in plastics, and 1,290 metric tons had other uses (e.g., ammunition primers, pigments) (USGS, 2002).

According to HSDB (2002), US imports of antimony trisulfide in 1986 were 34,794 lbs.

According to the EPA (1983a), antimony sulfide produced domestically or imported in 1980 included both refined antimony sulfide chemical and antimony sulfide ore (stibnite). All antimony sulfide chemical used domestically in 1980 (88,000 lb) was imported. Ninety-four percent of the stibnite used domestically in 1980 (12 million pounds) was imported and used to produce antimony oxide. The remainder (0.7 million pounds) was minded by the U.S. Antimony Corp., and used exclusively to produce sodium antimonite.

Antimony trisulfide is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (ChemID, 2002).

Producers and Importers:

According to Chemical Sources International, there are 26 US suppliers of antimony trisulfide (Chemical Sources International, 2002).

According to recent issues of chemical directories, antimony trisulfide is manufactured and/or distributed by Alfa Aesar/Johnson Matthey; Barium & Chemicals Inc.; Belmont Metals Inc.; CERAC, Inc.; Chemetall Chemical Products, Inc.; and NOAH Technologies Corporation (Chemcylopedia, 2002; Chemical Week Associates, 2002).

Use Pattern:

The first known use of black antimony sulfide, to manufacture vessels and vases, dates to 4000 BC with the Chaldeans. Antimony and its compounds are also among the oldest known medicinal remedies, having been used since biblical times. Plummer's pills, which contained sulfurated antimony, calomel, and guaiacum, with treacle, were prescribed for cutaneous eruptions, secondary syphilis, gout, apoplexy, and plethoric diseases. Doctors also used sulfurated antimony as a diaphoretic and alternative in scrofula, rheumatism, and cutaneous diseases (Winship, 1987).

According to the *Kirk-Othmer Encyclopedia of Industrial Chemistry*, antimony sulfide is an active filler in resinoid bonded abrasives (Rue, 1991). Antimony trisulfide is used in brake/clutch linings and fireworks (Ball *et al.*, 1996), in vulcanizing rubber (Criteria Group for Occupational Standards, 2000), and as a starting material for production of antimony and antimony compounds (Herbst *et al.*, 1985).

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Crude commercial antimony trisulfide can be used directly in the manufacture of matches or Bengal lights. For the production of high-quality pyrotechnics, e.g., electrically ignited detonators, the crude compound must be remelted in a reducing atmosphere at as slow a temperature as possible. A well-crystallized, readily ground product is obtained (Herbst *et al.*, 1985).

Antimony trisulfide, which reflects infrared radiation, is a constituent of camouflage paints. Burning antimony trisulfide emits a dense white smoke, which is used in visual fire control, marine markers, and visual signaling (Herbst *et al.*, 1985).

The vermilion or yellow antimony trisulfide is used as a pigment, in the manufacture of ruby glass, camouflage paints, and as an enamel compound (Lewis, 2002; Merck, 2001;Winship, 1987).

Currently, 260 patents on file with the US Patents and Trademark Office mention the use of antimony trisulfide in some capacity. Several patents refer to the use of this material as a non-asbestos friction material for brake pads (US Patents and Trademark Office, 2001).

^{99m}Te-antimony sulfide colloid is used for bone marrow imaging, lymphedema assessment, and scintigraphic mapping of lymphatic channels and sentinel nodes in melanoma and breast cancer. The colloidal particles have been reported as ranging from 3-30 nm (Tsopelas, 2001).

Antimony trisulfide, alone or in combination with other products, is used as a homeopathic remedy. It is sold in liquid, pellet, or tablet form for oral consumption (Health Canada, 2001).

Antimony sulfide photoconductors are used in vidicons for CCTV and for film service due to their higher sensitivity and better light reflection and dispersion characteristics (Burle Industries, 2001). These photoconductors are one of the most widely used in the medical field (MII/Teltron Technologies, Inc., 2001).

Human Exposure:

Occupational Exposure:

In industry, antimony enters the body almost entirely by inhalation of dust or fumes from processing or packing antimony compounds (McCallum, 1989).

The National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 26,669 workers, including 1,082 female workers, in 34 industries were potentially exposed to antimony trisulfide in the workplace (Sigma-Aldrich, 2001a). The NOES database does not contain information on the frequency, level, or duration of exposure to workers of any chemical listed therein. These figures also do not appear to reflect exposures from the mining of antimony sulfide ores.

According to Antimony Oxide Industry Association (AOIA) estimates published in 1983, the maximum number of workers exposed to any concentration of antimony substances is approximately 2,240. Another estimate of exposure to antimony sulfide provided to EPA was: a maximum of 11 workers at the US Antimony Corporation Montana facility, 220 workers at facilities which use antimony sulfide chemical, and an additional 1,710-1,880 workers engages in converting imported stibnite into antimony oxide (EPA, 1983a).

In a 1948 study, antimony levels in the blood or urine of two workers engaged in the crushing of refined Sb_2S_3 were below the unspecified limit of detection, although airborne concentrations were reported to be 42 and 52 mg Sb/m^3. In a 1955 study, mean urinary antimony concentrations were 68.4 ± 57 μg/L in Moroccan antimony mine workers exposed to Sb_2S_3 ore at concentrations ranging from 12-36 mg Sb/m^3 (Ball *et al.*, 1996).

In a 1988 study, antimony concentrations in lung tissues from deceased workers who had been exposed to antimony oxides and sulfides and other compounds at a Swedish smelter (0.26 μ/g wet weight) were significantly higher than those in rural control subjects (0.03 μg/g) and urban control subjects (0.02 μg/g). These concentrations were not influenced by length of retirement. Prolonged retention of antimony was also suggested in another report in which the urinary concentration of 55 μg Sb/L, found 7 months after retirement of an antimony process worker with pneumoconiosis, decreased to 28 μg Sb/L four years later (Ball *et al.*, 1996).

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Environmental Exposure:

Antimony can enter the human body from a variety of sources. Data on concentrations of antimony in the blood and urine of individuals not occupationally exposed to antimony appear to reflect the analytical method employed. Mean values for blood are 0.7-85 μg/L and for urine they are <1.0-6.2 μg/L. Antimony levels below 0.032 μg/g enamel were detected in teeth from Neolithic man, increasing to 1.59 μg/g in Middle Ages man, and decreasing to <0.006 μg/g at present time (Ball *et al.*, 1996; Berg & Skyberg, 1998).

Data on daily intake of antimony are also inconsistent, possibly reflecting differences in analytical techniques. Reports range from 10 μg in a Swedish study to 250-1,250 μg in a US study on institutional diets for children (Elinder & Friberg, 1979).

The maximum daily intake from water has been reported to be 15 μg, assuming a mean water consumption of 1.5 L/d and maximum tap water concentrations of 10 μg/L (Winship, 1987).

In the National Health and Nutrition Examination Survey, the geometric mean of antimony concentrations in the urine of 912 US residents, aged 6 years and older, was 0.10 (0.09-0.12) μg/L (CDC, 1999).

Consumer Exposure:

Crayons, watercolors, and water-based paints were investigated to determine the migration of antimony and other metals under defined conditions of European Standard EN 71-3. A total of 48 products from China, Taiwan, Japan, United States, and the European Union were examined. Antimony (0.17-0.49 ppm) migrated from 17% of the samples. Migration occurred from crayons and watercolors (Rastogi & Pritzl, 1996).

Environmental Occurrence:

Antimony occurs in the earth's crust at a concentration of 0.2-0.3 ppm. It is found in more than 100 minerals, but is mined mainly from stibnite (Sb_2S_3), kermesite (2 Sb_2S_3 Sb_2O_3), alentinite (Sb_2O_3), cervantite (Sb_2O_4), stibiconite (Sb_2O_4 $2H_2O$, tetrahedride [Cu Fe]$_{12}$ Sb_4S_{13}), jamesonite (Pb_4Fe Sb_6S_{14}), and pyrargyrite (Ag_3SbS_3) (Léonard & Gerber, 1996).

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Stibnite is mined primarily in Bolivia, South Africa, and China. Total world reserves of antimony were estimated in 1988 to be 4.35 million metric tons (Berg & Skyberg, 1998).

Antimony has been found in rivers, soil, and ambient air. In soil, antimony ranges from 0.1-10 mg/kg dry weight. The concentration of antimony in fresh and seawater is about 0.2 mg/m3 and concentrations up to 100 ppm are found in plants. In the Rhine River, antimony averages 0.1 µg/L; 0.2 µg/L has been reported in the northeastern Pacific Ocean (Elinder & Friberg, 1979; Léonard & Gerber, 1996; Winship, 1987).

In freshwater fish, antimony concentrations have been reported to be on the order of 3 µg/kg (Elinder & Friberg, 1979).

The natural and man-made emissions of antimony are estimated at 950 tons from continental dust flux, 30 tons from volcanic dust flux, 20,000 tons from industrial emissions, and 18,000 tons from fossil fuel flux. Up to 270 ±140 µg/g antimony has been found in incinerator fly ash and in suspended particles from coal combustion (Léonard & Gerber, 1996).

Atmospheric concentrations of antimony have been reported to be 0.6 ng/m3 in rural areas and 15-8,236 ng/m3 in urban areas of North America (Léonard & Gerber, 1996). Concentrations of antimony in Chicago air averaged 32 ng/m3 (1.4-55) ng/m3 (Elinder & Friberg, 1979).

Measurements of antimony in air suggest a daily intake of 4.4-72 ng/d, which is insignificant compared with intake from diet (Winship, 1987).

Regulatory Status:

Both the Mine Safety and Health Administration (MSHA) and the Occupational Safety and Health Administration (OSHA) permissible exposure limit for antimony compounds is 0.5 mg/m^3 averaged over an eight-hour work shift. The NIOSH recommended exposure limit (REL) for antimony compounds is 0.5 mg/m^3 averaged over a ten-hour work shift (HSDB, 2002; Sigma-Aldrich, 2001a). The American Conference of Governmental Industrial Hygienists (ACGIH)-recommended threshold limit value (TLV) for antimony compounds is a time-weighted average (TWA) of 0.5 mg/m^3 (ACGIH, 2001).

Antimony trisulfide is listed as a hazardous air pollutant (HAP) generally known or suspected to cause serious health problems under the Clean Air Act, as amended in 1990, and is subject to Superfund Amendments and Reauthorization Act (SARA) Section 313 reporting requirements (HSDB, 2002; Sigma-Aldrich, 2002a).

Toys in European Union markets must conform to the EEC Directive on safety of toys. One restriction concerns bioavailability of several toxic metals from toy materials, including paints, paint coatings, papers, textiles, and materials used for writing and drawing. The maximum limits for bioavailability per day from the accessible parts of a toy are set to 0.5 µg for antimony (Rastogi & Pritzl, 1996).

In the Fourth Report of the Interagency Testing Committee (ITC) (44 FR 31866-31889, June 1, 1979) (EPA, 1979), antimony sulfide was considered, along with antimony oxide and antimony metal.   The ITC recommended testing for carcinogenicity, mutagenicity, teratogenicity, chronic effects, environmental effects, and epidemiology. The EPA responded to the ITC on January 6, 1983 (48 FR 717) as described in the Twelfth Report of the Interagency Testing Committee to the Administrator (48 FR 24443) (EPA, 1983b).

EPA indicated that the Agency did not intend to initiate rulemaking based on its analysis of existing data and preliminary acceptance of a program submitted by the Antimony Oxide Industry Association (AOIA). According to EPA, the testing program sponsored by the AOIA would expeditiously provide more information than initiating rulemaking (48 FR 39979). The study plans for the AOIA Program included a 90-day subchronic inhalation study of antimony oxide, a chronic/oncogenic inhalation study of antimony oxide, aerobic and anaerobic biodegraation studies of antimony oxide, and sediment sorption studies of antimony oxide (48 FR 39981). The Negotiated Testing Agreement for antimony compounds did not contain testing plans for antimony sulfide based, in part, on the AOIA argument that less worker exposure is likely to antimony metal and antimony sulfide than to antimony oxide (48 FR 39980) (EPA, 1983c). .

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

IARC has concluded that there is limited evidence that antimony trisulfide is carcinogenic to experimental animals. Antimony trisulfide was considered "not classifiable" as to its carcinogenicity to humans (Group 3) (IARC, 1989).

Human Data: No epidemiological studies or case reports specifically investigating the association of exposure to antimony trisulfide and cancer risks in humans were identified in the available literature. Studies of smelter workers and glass factory workers may have some relevance although other antimony compounds, e.g., antimony oxide, were also present. These studies are further confounded by the presence of other metals or metalloids, especially arsenic, so that the risks observed in the study populations cannot be attributed solely to antimony.

In a group of Newcastle, England, smelter workers exposed to antimony sulfide ore concentrates and antimony oxide before 1961 and followed from 1961-1992, 32 deaths due to lung cancer occurred vs 14.7 expected. The increased incidence of lung cancer was too large to attribute to smoking. Until 1972, the company also produced antimony-arsenic alloys for the battery industry from byproduct slags, and arsenic appears to have been a factor in the lung cancer excess (Berg & Skyberg, 1998; McCallum, 1989).

In a mortality study of 1,014 workers employed at a Texas antimony smelter between 1937 and 1971, a standardized mortality ratio (SMR) of 1.39 for lung cancer was observed. Although this SMR was not statistically significant, a positive trend with increasing duration of employment was significant. Airborne antimony levels measured by NIOSH in 1975 and 1976 were 0.05-6.2 mg Sb/m^3; arsenic levels were 0.001-0.047mg/m^3. The excess of lung cancer was also confounded by the presence of other metals and smoking (Schnorr *et al.*, 1995).

Although antimony ores and ore concentrates contain stibnite, antimony oxide exposures to airborne antimony that occur during heat processing would generally involve antimony oxide, so the study results are not easily attributed to antimony trisulfide.

In the art glass industry, where powdered antimony compounds are used, workers are at increased risks of dying from several types of cancer, cardiovascular diseases, and

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cerebrovascular diseases. For colon cancer, a clearly increasing trend in risk was observed with increasing use of antimony, and to some extent also with increasing use of lead. No obvious correlation with any metal could be found for lung cancer (Ball *et al.*, 1996; Berg & Skyberg, 1998; Léonard & Gerber, 1996; Wingren & Axelson, 1993).

Signs and Symptoms of Antimony Poisoning in Humans: The signs and symptoms of acute and chronic antimony poisoning are similar to those of arsenic poisoning (Winship, 1987).

Acute Toxicity in Humans:
A 24-year old woman ingested an unknown quantity of antimony trisulfide. Clinical examination one hour later was normal although the patient complained of slight epigastralgia and dysphagia and a metallic taste in the mouth. A gastric lavage was performed immediately, followed by forced diuresis and dimercaprol therapy. The patient did not develop clinical signs and routine biological tests remained normal; she was discharged from the hospital on day 6 (Bailly *et al.*, 1991).

Accidental antimony poisoning has been reported following the use of old porcelain houseware. It was assumed that the acidity of the drinks released sufficient antimony to cause the toxic effects (Winship, 1987).

Subacute Exposure of Humans to Antimony Compounds: Subacute exposure has caused headache, coughing, vomiting, joint or muscular pain, sleeplessness, vertigo, and loss of appetite. Antimony produces gastrointestinal irritation more rapidly than arsenic, and vomiting is more prominent. The toxic effects of trivalent antimony have been described as greater than those of the pentavalent form, and antimony trisulfide has been suggested to be more toxic than antimony oxide (Winship, 1987).

Animal Data:
Acute Studies: According to the UK Health & Safety Executive (HSE), antimony trisulfide has been investigated in a series of modern, well-conducted acute toxicity studies. A group of 10 Wistar rats exposed (nose-only) for 4 hours to 5,000 mg/m3 Sb_2S_3 (3,600 mg/m3 Sb) (particle diameter 4.6 μm) developed black foci in the lungs, deaths or other treatment-related effects did not occur over a 15-day observation period. A dose of 2,000 mg/kg Sb_2S_3 (1,440 mg Sb/kg) administered to groups of 10 Wistar rats by gavage or applied to the intact skin for 24 hr under an occlusive dressing caused no deaths or signs of toxicity during a 15-day observation period (Ball *et al.*, 1996).

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Subacute/Subchronic Studies: Ten male and ten female Sprague-Dawley rats were exposed to an antimony sulfide ore at 1,700 mg Sb/m3 for 1 hr, 1-6 times every 2 months, for up to 12 months.   After the first exposure, the animals developed acute transitory pneumonitis.   No appreciable inflammation was seen in the lungs of any animal at the end of the study, although periodic sacrifice revealed deposits of dust laden phagocytic cells within the alveolar septae (Cooper *et al.*, 1968, cited in Ball *et al.*, 1996).

Breiger and coworkers (1954) conducted a series of experiments on dust collected from a factory in which Sb_2S_3 was used to manufacture resinoid grinding wheels.   The amount of antimony in the factory dust is not known.   Exposures were carried out for 7 hr/d, 5 d/wk; 10 rats and 11 rabbits were exposed for 6 wk at 3.1 mg/m^3 and 5.6 or 28 mg/m^3, respectively; 4 dogs were exposed at 5.5 mg/m^3 for either 7 wk or 10 wk with a "several week" recovery period.   Non-specific ECG changes observed in all animals consisted of elevations in the RS-T segment and flattening of T-waves.   The main pathologic finding was dilation of the heart with flabby myocardium.   These changes were least marked in the dogs.   Rabbits exposed at the higher dose also had evidence of parenchymal degeneration in the liver and lung inflammation (cited in Criteria Group for Occupational Standards, 2000, and Ball *et al.*, 1996).

Chronic/Carcinogenicity Studies: No 2-year carcinogenicity studies of pure antimony trisulfide were identified in the available literature.

Groth and coworkers (1986) examined the carcinogenicity of antimony ore concentrate in Wistar rats, 90 males and 90 females per group.   The mass median diameter (MMAD) of the particles was 2.22 microns.   Animals were exposed at 36 or 40 mg/m^3 for 7 h/d, 5 d/wk for up to 52 weeks.   Fifteen males and 15 females were killed between 6 and 12 months after initial exposure; the rest were killed 18-20 weeks after the end of the exposure period. Interstitial fibrosis and alveolar-cell hyperplasia and metaplasia were observed in both males and females.   Seventeen of the 68 females surviving at the time the first lung tumor was observed developed lung tumors vs none in the control group ($p<0.001$).   Lung tumors were not seen in male rats even though their lungs contained higher antimony concentrations.

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The ore concentrate studied by Groth and his associates contained 46% antimony, principally antimony trisulfide (stibnite), <4% titanium, 0.5% aluminum, 0.2% tin, 0.3% lead, 0.3% iron, and 0.08% arsenic (IARC, 1989). Although antimony was found in the lungs, arsenic was also present (Berg & Skyberg, 1998).

Short-Term Tests: No information on the genotoxicity of antimony trisulfide, a relatively insoluble compound, was found in the available literature.

Metabolism:

Exposure of female dogs by inhalation to about 5.5 mg/m^3 antimony trisulfide dust from a smelter (particle size <2 m) for ten weeks resulted in urinary excretion of up to 16-18 mg/L antimony (Brieger *et al.*, 1954).

Measurements of antimony in lung tissue from previously exposed smelter workers showed that inhaled antimony can be deposited and retained in the lung for several years (Winship, 1987). If absorbed, antimony compounds accumulate in vascularized organs and tissues, primarily the liver and the kidneys (Gebel, 1997). Unlike arsenic, antimony does not appear to be methylated *in vivo* (Bailly *et al.*, 1991).

Other Biological Effects:

Toxicity to the Heart:

Brieger *et al.* (1954) reported increased mortality and morbidity from heart disease in abrasives industry workers. A total of 124 workers were exposed to antimony trisulfide at air concentrations ranging from 0.6-5.5 mg/m^3 for 8-24 months. During this period six workers died suddenly and two others died of chronic heart disease. Four of the deceased were under 45 years of age. ECG changes, mostly of the T-wave, were seen in 37 of 75 workers examined. In the 16 years preceding introduction of antimony, only one death had occurred in this department. After antimony trisufide use was discontinued, no new deaths due to heart disease and no abnormal increase in heart/circulatory problems were reported, although the ECG changes persisted in 12 workers. As Berg and Skyberg (1998) note, a cohort age effect cannot be ruled out, thus, any estimation of coronary heart risk from antimony exposure is not possible. The lack of a control group further limits interpretation of the study results.

Other studies where workers received combined exposures to antimony trisulfide and antimony oxide do not confirm the findings of Brieger's group. McCallum (1967)

reported that the number of deaths from heart disease male antimony workers in the Newcastle factory were lower than or equal to expected values in the region. Schnorr and coworkers (1995) found no statistically significant increases in mortality from ischemic heart disease in a study of 1,014 workers employed at an antimony smelter in Texas.

The effects of factory dust containing antimony trisulfide on the hearts of experimental animals was described in the subsection entitled *Subacute/subchronic toxicity*.

Respiratory System Toxicity: Of a total of 100 miners exposed to antimonite dust concentrations considerably exceeding the Russian MAC, 16 showed evidence of chronic bronchitis although no pneumoconioses were observed (Lobanova *et al.*, 1996). The degree to which the bronchitis was related to the effects of arsenic and not antimony exposure alone, remains unsettled (Berg & Skyberg, 1998).

Of the Newcastle, England, antimony smelter workers described previously in the subsection, Human Data, 44 of 262 men had signs of simple pneumoconiosis observed on X-rays of the lungs. A significant association between employment duration and antimony content in the lungs was observed, as was an increase in radiographic category with increasing length of employment. Exposures to other antimony compounds and arsenic are confounding factors in the study (Berg & Skyberg, 1998; McCallum, 1989).

X-ray examinations of 28 workers employed 1-15 years at the Texas smelter described previously in the subsection, Human Data, showed conclusive evidence of pneumoconiosis in three with five suspected cases. Crude antimony sulfide ore was refined to antimony oxide, and airborne concentrations of antimony were estimated to be 0.081-75 mg/m^3 in 1966 (Cooper *et al.*, 1968).

Other workers involved in crushing refined antimony trisulfide did not show X-ray evidence of adverse lung effects although airborne concentrations were estimated to be 30-37 mg Sb/m^3. Antimony was not detected in the blood or urine of these workers (Bulmer & Johnston, 1948, cited in Ball *et al.*, 1996). Whether these inconsistent results are simply a reflection of older, less sensitive measurement techniques is not clear from the available information.

Skin Effects: Pustular skin eruptions, "antimony spots", have been described as common among persons who have worked with antimony and antimony salts in the past. These eruptions were transient and mainly affected skin areas exposed to heat and those where sweating occurred (Elinder & Friberg, 1979). Some investigators believe that "antimony spots" are not caused by antimony but by arsenic trioxide (Berg & Skyberg, 1998).

Other Organs: Degenerative changes in the liver and in the tubular epithelium of the kidney were observed in rabbits exposed to antimony trisulfide at 27.8 mg/m^3 for five days (HSDB, 2002).

Enzyme Induction: Antimony and antimony-containing parasiticidal drugs, especially trivalent antimony, have been shown to be potent inducers of heme oxygenase in liver and kidney in rats. This effect was dose-dependent and independent of the salt used (Winship, 1987). The relevance of this information to antimony trisulfide is not clear.

Structure-Activity Relationships:

Antimony belongs to the same periodic group as arsenic, which it resembles both chemically and biologically. Both metalloids act as clastogens but do not have mutagenic properties. Arsenic was shown to cause aneuploidy and aneugeny, indicating reactivity to the spindle apparatus of the cell. Whether antimony acts aneugenically is not known. Their trivalent species are responsible for the mediation of their toxicological effects (Elinder & Friberg, 1979).

Arsenic, a well-recognized carcinogen, is metabolised via reduction, glutathione (GSH) conjugation, and subsequent methylation in mammals. There are major species differences. In contrast, evidence of antimony methylation in mammals is low and quantities of antimony changing valency after incorporation seem to be small. The affinity of antimony to thiol residues and its potency to provoke DNA-protein crosslinks seems to be far lower than it is for arsenic (Gebel, 1997).

No carcinogenicity bioassays meeting modern regulatory standards have been conducted for any antimony compound. Antimony trioxide has been evaluated in three studies involving a one-year exposure period.

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1. Male and female F344 rats exposed to 0, 0.05. 0.5, and 5 mg antimony trioxide (purity >99%; MMAD 3-4 μm) for 6 hr/d, 5d/wk for 12 months followed by a 12-month recovery period did not develop treatment related tumors although fibrosis and chronic interstitial inflammation were observed (Newton *et al.*, 1994).

2. In an earlier study, male and female Wistar rats were exposed to 0 or 45.5 mg/m3 (36 mg/m^3 as Sb) antimony trioxide (MMAD 2.8 μm) for 5 hr/d, 7 d/wk for 12 months and allowed to recover for 4 months. Treatment-related lung tumors were observed in 19 females (27% of those still alive at the time of first tumor), including bronchoalveolar carcinomas, squamous cell carcinomas, and scirrhous cell carcinomas. Fibrosis was observed in both sexes, but the females had a greater incidence of alveolar cell metaplasia (Groth *et al.*, 1986).

3. CDF female rats were exposed to antimony oxide (purity 99.4%, 0.02% arsenic, 0.20% lead; particle diameter 0.4 ± 2 μm) at 0, 1.6, or 4.2 mg Sb/m^3 for 6 h/d. 5 d/wk for 1 year with a 1-year recovery period. Lung tumors observed included 13/16 with adenomas and 2/16 with squamous carcinomas including one animal with both, all in high dose animals, and fibrosis in animals at both high and low doses (Watt 1980, 1983; cited in Ball *et al.*, 1996).

    An earlier study by Gross and coworkers exposed "young" male SD rats at 100-125 mg/m^3 fpr 25hr/wk for 14.5 months. No lung tumors were reported (Gross et al, 1965; cited in NIOSH, 2002).

Antimony trioxide was negative in the Ames *Salmonella* assay when tested with and without metabolic activation in strains TA98, TA100, TA1535, and TA1537. Antimony trioxide was also negative in *E. coli* WP2 and WP2 uvra assays with and without S-9 using the preincubation and the standard plate techniques. This substance was negative in the mouse lymphoma L5178Y (TK+/TK-) with and without S-9, and it was also negative for unscheduled DNA synthesis in the *in vivo* rat liver DNA repair assay (CCRIS, 2002).

Antimony trioxide was reported to be positive in the rec-assay using *Bacillus subtilis* (H17 vs M45) and in SCE assays using V79 cells (Kada *et al.*, 1980; Kanematsu *et al.*, 1980; Kuroda *et al.*, 1991). Antimony trioxide was also reported to be clastogenic when administered by gavage to mice, the frequencies of chromosomal aberrations

induced being directly proportional to dose and duration of exposure (Gurnani *et al.*, 1993). A more recent study reported a positive response in an *in vitro* cytogenetic assay using isolated human peripheral lymphocytes but not in any *in vivo* assays (see above) causing the authors to question the earlier results (Elliott *et al.*, 1998).

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