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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR ANTIMONY AND COMPOUNDS

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with antimony and compounds. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Antimony. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-020. NTIS No. PB81-117319.

U.S. EPA. 1983a. Reportable Quantity Document for Antimony and Compounds. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for Antimony Potassium Tartrate. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983c. Reportable Quantity Document for Antimony Trioxide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985a. Health and Environmental Effects Profile for Antimony Oxides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for antimony. Online. (Verification date 11/6/85). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

RfD_O values were derived for antimony and selected compounds based on a LOAEL for antimony of 350 µg/kg/day associated with potassium antimony tartrate in the drinking water of rats for lifetime exposure (Schroeder et al., 1970). Reduced lifespan was observed in both sexes and altered blood biochemistries were observed in males. The only concentration tested was 5 ppm antimony. RfD_O values for antimony of 24.5 µg/day, for antimony potassium tartrate of 65.48 µg/day and for antimony tri-, tetra- and pentoxides of 29.3, 30.9 and 32.5 µg/day, respectively, were calculated. Because adequate subchronic oral data were not located, an RfD_{SO} value was not developed. It should be noted that orally administered antimony has been inadequately tested for carcinogenicity.

RfD_I and RfD_{SI} values were not derived because of data suggesting that antimony is carcinogenic in rats following inhalation exposure. However, the data were inadequate for quantitative risk assessment (Watt, 1980, 1981, 1983; ASARCO, Inc., 1980).

Watt (1980, 1981, 1983) and ASARCO, Inc. (1980), in reports of the same study, observed a statistically significant increase in the incidence of lung tumors in rats exposed to antimony trioxide by inhalation. In addition, Wong et al. (1979) noted an increased incidence of lung cancer in rats exposed by the inhalation route to animony trisulfide. This observation coupled with indications that occupational exposure to antimony processing is associated with lung cancers in humans (Davies, 1973) is qualitative evidence for the carcinogenicity for antimony by inhalation. However, the Davies (1973) report is only available in the form of a 2-page letter making it impossible to thoroughly evaluate this data. An earlier U.S. EPA (1983f) analysis concluded that the animal data were insufficient for quantitative estimation of the carcinogenic potency of antimony.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RMCL	Recommended maximum contamination levels
RV_d	Dose-rating value
RV_e	Effect-rating value
SNARL	Suggested-no-adverse-response level
TLV	Threshold-limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Antimony is a metalloid that belongs to Group V-A of the periodic table and has oxidation states of +3, +5 and -3; however, the -3 state is not stable in oxygenated water (U.S. EPA, 1980a). Antimony ore bodies are small and scattered throughout the world. Well over a hundred minerals of antimony are found in nature. Occasionally native metallic antimony is found, but the most important source of the metal is the mineral stibnite, antimony trisulfide (Carapella, 1978). Selected physical properties of antimony and some of its compounds are listed in Table 1-1.

Most of the available data concerning exposure to antimony substances do not distinguish between antimony metal, antimony trioxide and antimony trisulfide. Antimony is expected to exist as the trioxide in the atmosphere, however, since most of the atmospheric releases of antimony substances result from high temperature industrial processes, from the combustion of petroleum, petroleum products and coal, and from the incineration of products that contain antimony. At the high temperatures used in these processes, oxidation of the antimony substances occurs, resulting in the formation of antimony trioxide (and possibly also antimony tetraoxide and antimony pentoxide) (U.S. EPA, 1985a).

The antimony released from high temperature processes condenses rapidly onto suspended particulate matter and will associate predominantly with small diameter particles (e.g., 1 nm in size), which are not only difficult to trap with conventional stack technology, but also tend to settle out less rapidly and thus are transported greater distances through the atmosphere. The estimated residence time of antimony particulates in the atmosphere ranges between <30 days to ~40 days, which is much longer than the atmospheric residence time of most particulates (<1 week) (U.S. EPA, 1985a).

TABLE 1-1

Selected Physical Properties of Antimony and Some of Its Compounds[a]

Compound	CAS Number	Empirical Formula	Molecular Weight	Form	Melting Point (°C)	Boiling Point (°C)	Water Solubility
Antimony	7440-36-0	Sb	121.75	silver-white metallic, hexagonal	630.5	1750	insoluble
Antimony pentoxide	1314-60-9	Sb_2O_5	323.50	yellow powder	380[b], 930[c]	NA	slightly soluble
Antimony tetraoxide	1332-81-6	Sb_2O_4	307.50	white powder	-0, 930	NA	slightly soluble
Antimony trioxide	1309-64-4	Sb_2O_3	291.50	white, cubic; colorless rhombic	656	1550 (cubic form sublimes)	5 mg/ℓ (25°C)[d]
Antimony trisulfide	1345-04-6	Sb_2S_3	339.69	black rhombic; yellow-red amorphous	550	~1150	1.75 mg/ℓ (18°C)

[a]Source: Weast, 1983

[b]At 380°C, antimony pentoxide loses one oxygen atom to become antimony tetraoxide.

[c]At 930°C, antimony pentoxide loses two oxygen atoms to become antimony trioxide.

[d]Taken from U.S. EPA, 1985a

NA = Not available

In water, some photochemical reduction to metallic Sb and Sb_2O_5 of both suspended prismatic and rhombic antimony trioxide occurs upon irradiation at wavelengths >290 nm. The antimony metal from the rhombic form is readily oxidized back to antimony trioxide in oxygenated waters, while the prismatic form darkens because there is no facile oxidation of the dark antimony metal in the crystal lattice. It appears that very little of the antimony oxides in water occurs in the dissolved state, and that which does dissolve is present as various hydrolysis products such as $Sb(OH)_3$ and $HSbO_2$. The vast majority of antimony species in water systems are in the form of various suspended particulates that tend to settle onto sediments over time. The rate of removal from water by precipitation or by precipitation and settling depends on such factors as salinity, changes in pH and amount of current or turbulence present in the water systems. Antimony associated with particulates would therefore be expected to accumulate, for example, where contaminated rivers flow into reservoirs, lakes, delta areas and other areas where sediments are actively being deposited, such as inside of bends in rivers. The potential for this accumulation increases as the source(s) of the antimony material is approached. Bioconcentration of antimony species other than metallic antimony has been shown to be insignificant for most aquatic species; however, a report of a BCF of 16,000 for freshwater and marine invertebrates indicates that bioconcentration may be significant for some species; biomagnification of antimony materials was not observed (U.S. EPA, 1985a).

In soil, trace metals including amtimony reportedly have been found as water soluble species in the interstitial water, precipitates and coprecipitates as oxides, exchangeable species absorbed onto soil surfaces and organically bound species, and also within mineral crystal lattices; however, the

amount of water soluble species is not expected to be significant for the antimony oxides. Precipitation and coprecipitation as oxides (antimony tri-, Sb_4O_6 and tetraoxide) have been suggested as important processes by which antimony is retained on soil surfaces.

Antimony trioxide, and presumably tetra- and pentoxide, is apparently persistent in soil, which is to be expected from its low water solubility, lack of reactivity, stability and low vapor pressure. It is expected that antimony substances will accumulate in the soil and sediment near production and processing facilities, as well as at or near disposal sites (U.S. EPA, 1985a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Felicetti et al. (1974a) administered solutions of tri or pentavalent ^{124}Sb compounds by gavage to Syrian hamsters. Hamsters were whole body counted daily until sacrifice on day 4 postexposure. Six hamsters were dosed with 1 mℓ of solution containing 2 μCi/mℓ ^{124}Sb. Two hamsters were dosed with 2 mℓ of solution containing 2 μCi/mℓ. The animals dosed with the 2 mℓ volume received trivalent ^{124}Sb, two of the six hamsters receiving a 1 mℓ volume received trivalent ^{124}Sb while the remainder received pentavalent ^{124}Sb. The two animals receiving 2 mℓ of trivalent ^{124}Sb retained 15% and 9% of the initial body burden by day 4, of which 88 and 90%, respectively, was found in the GI tract. The median values for retention of day 4 for the remaining animals was 1.6% for those receiving the trivalent compound and 2% for those receiving the pentavalent of which 61 and 64% were found in the GI tract. The investigators concluded that "very little" of these compounds were absorbed from the GI tract, probably <1% (Felicetti et al., 1974b).

U.S. EPA (1980a) noted that these forms were the relatively insoluble oxides and that water-soluble organic derivatives may be absorbed to a greater extent. Elinder and Friberg (1977) reported that ~15% of a tartar emetic (potassium antimony tartrate) was absorbed by the gastrointestinal tract of mice. Further data were not available in the secondary source from which this study was taken.

2.2. INHALATION

Belyaeva (1967) found detectable levels of antimony in the placenta, amniotic fluids and cord blood of pregnant women working in antimony

smelters during pregnancy. These data indicate that absorption does occur from the human respiratory tract, but estimations of quantity or rate are not possible.

Felicetti et al. (1974a) exposed Syrian hamsters to aerosol of tri- or pentavalent ^{124}Sb antimony compounds and subjected the animals to whole body scintillation counting until sacrifice on day 0 to day 32 postexposure. The detection of radioactivity in several internal organs, the pelt and the urine suggest that absorption from the pulmonary tract occurred, but estimation of the quantity of the dose absorbed is not possible. Based on the data discussed in Section 2.1., it appears that gastrointestinal absorption of radioactivity cleared from the pulmonary tract by mucociliary action should have contributed little to the levels of radioactivity detected in internal organs.

Felicetti et al. (1974b) exposed beagle dogs by nose only to aerosol of ^{124}Sb from an antimony tartrate complex. Aerosol formation at three different temperatures, 100, 500 and 1000°C, resulted in production of particles with activity median aerodynamic diameters of 1.3, 1.0 and 0.3 μ, respectively. Regional body counting immediately after exposure indicated that the 100°C aerosol had deposited in the nasopharynx and the lung and that the smaller particles found at higher temperatures had deposited mainly in the lungs. The detection of radioactivity in the pelt and several internal organs on sacrifice at 32-128 days postexposure indicated that absorption from the pulmonary tract did occur. It was not possible to estimate the properties of the inhaled dose that was absorbed or the contribution to radioactivity in the tissues resulting from gastrointestinal absorption of antimony cleared from the pulmonary tract by mucocilliary action.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Although the following two studies (Dunn, 1928; Monier-Williams, 1934) reported acute poisoning incidents in humans, they were considered in the risk assessment (U.S. EPA, 1985a) and therefore are reported here. Seventy people who drank lemonade from preparations left overnight in white enamelware buckets (the enamel contained 2.88% antimony trioxide) became ill. Antimony trioxide had been leached from the enamel by the acidic lemonade. Fifty-six people were hospitalized, suffering from burning stomach pains, colic, nausea and vomiting; most recovered within 3 hours. Analysis found that the lemonade contained 0.013% metallic antimony. Each person ingesting ~300 mℓ lemonade would have received 36 mg antimony, which is similar to an emetic dose listed in the British Pharmacopoeia.

Several subchronic and chronic oral studies with various forms of antimony are briefly summarized in Table 3-1. Subchronic oral studies include Sunagawa (1981), Bradley and Frederick (1941), Smyth and Carpenter (1948), and Gross et al. (1955). However, in the Bradley and Frederick study, effects for individual exposure groups were not discussed.

Smyth and Carpenter (1948) gave rats dietary antimony trioxide at doses ranging from 60-1070 mg/kg bw/day for 30 days and observed reduced growth and appetite as well as unspecified micropathology of the liver, kidney, spleen or testes at the highest dose. No effects were observed at 270 mg/kg/day. Sunagawa (1981), however, noted a significant decrease in erythrocyte counts in rats fed diets containing 5000 ppm metalic antimony for 6 months. Assuming a food factor for rats of 0.05, an equivalent intake of 250 mg/kg/day is estimated.

TABLE 3-1

Summary Table for Subchronic Toxicity of Antimony and Compounds

Route	Compound	Species/ Strain	Sex	No. at Start	Vehicle	Exposure or Dose	Response	Reference
Oral	antimony metal	rat/NS	NS	NS	diet	5000-20,000 ppm for 24 weeks	Significant decrease in erythrocytes at 5000 ppm	Sunagawa, 1981
	antimony trioxide	rat/ Wistar	M,F	5/sex	diet	60-1070 mg/kg bw/day for 1 month	Reduced growth and appetite; unspecified micropathology of the liver, kidney, spleen or testes at highest dose, no effect at 270 mg/kg/day	Smyth and Carpenter, 1948
	antimony trioxide	rat/NS	NS	NS	diet	1.0-2.0% (10,000-20,000 ppm) for 24 weeks	Changes in enzymes and blood parameters	Sunagawa, 1981
	antimony trioxide	rat/NS	NS	20	diet	2.0% (20,000 ppm) for 8 months	Decreased body weight	Gross et al., 1955
Inhalation	antimony trioxide	rat/NS	NS	NS	dust	250 mg/m³ for 4 hours/ day for 1.5-2.0 months	Lung, liver, kidney, pancreatic changes; uterine and ovarian changes	Belyaeva, 1967
	several antimony compounds*	rat/NS	NS	NS	dust	2-4 hours/day for 6 months*	Lipoid pneumonia, deep morphological changes in the lung	Gudzovskii, 1968
	antimony trioxide	guinea pig	NS	24	dust	45.4 mg/m³, 2-3 hours/ day for ~265 days	Pneumonitus, subpleural hemorrhage, liver degeneration, splenic damage, blood alterations	Dernehl et al., 1945
	antimony trioxide	rats/ Sprague-Dawley	M	50	dust	100-125 mg/m³, 25 hours/ week for 14.5 months	Lipoid pneumonia	Gross et al., 1952
	antimony trioxide	rat	F	NR	dust	1.6 (±1.5) or 4.2 (±3.2) mg/m³ antimony for 6 hours/day, 5 days/week for 1 year followed by 1-year observation period	Lung fibrosis and hyperplasia that were both dose- and duration-related	Watt, 1980, 1981, 1983; ASARCO, Inc., 1983

*Metallic antimony at 4.9 mg/m³, antimony trioxide at 50 mg/m³, antimony trisulfide at 237 mg/m³, antimony pentasulfide at 257 mg/m³

NS = Not specified; NR = not reported

3.1.2. Inhalation. Several subchronic inhalation experiments with antimony trioxide dust in laboratory animals are summarized in Table 3-1. These studies (Belyaeva, 1967; Gudzovskii, 1968; Dernehl et al., 1945; Watt, 1983; Gross et al., 1952) failed to identify a NOAEL but indicated that the lung is the primary target organ by inhalation exposure. At high levels of exposure (250 mg/m^3, 4 hours/day for 1.5-2.0 months), histopathological lesions were also noted in the liver, kidney, pancreas, uterus and ovary (Belyaeva, 1967).

3.2. CHRONIC

3.2.1. Oral. Rats exposed to antimony showed a significant decrease in longevity ($p<0.001$), which was defined as the mean survival time for the last 10% of the surviving animals. Kanisawa and Schroeder (1969) reported similar results in mice.

Only two studies of the chronic oral toxicity of antimony compounds were located in the available literature. These experiments, summarized in Table 3-1 are a lifetime study with rats (Schroeder et al., 1970) and a lifetime study with mice (Kanisawa and Schroeder, 1969) in which drinking water contained 5 ppm antimony from potassium antimony tartrate. The Kanisawa and Schroeder (1969) study was designed primarily as a cancer bioassay; therefore, other indicators of toxicity were either not examined in detail or not reported. Only visible tumors were sectioned, however. Body weights were monitored and no significant differences found. The authors estimated that the mice drank 7 mℓ water/100 g body weight, which corresponds to 35 µg/100 g or 350 µg/kg.

In the Schroeder et al. (1970) study, rats were exposed to 5 ppm antimony in their drinking water. Endpoints monitored included body weights, blood pressure, serum chemistries including glucose, and urinalysis.

Animals dying during the study were subjected to autopsy and grossly visible lesions were examined histopathologically. Both males and females exhibited significantly decreased longevity. Fasting serum glucose levels were not significantly different from controls in either sex. Nonfasting serum glucose was depressed significantly in both sexes. No effects were seen on blood pressure. Urinalysis did not reveal statistically significant differences. The authors do not report water consumption in this study; however, Kanisawa and Schroeder (1969) report water consumption for rats of the same strain handled in the same laboratory as 7.5 mℓ/100 g for females and 6.8 mℓ/100 g for males. These drinking rates would correspond to an estimated dose of 350 μg/kg bw/day. The finding of reduced longevity appears to be the most biologically significant finding. Failure to perform a complete histopathological workup is seen as a major deficiency in this study along with the single dose level and minimal reporting detail.

3.2.2. Inhalation. Chronic inhalation studies include a 2-year experiment with rats using antimony trioxide (Watt, 1983) and occupational studies with antimony trioxide (McCallum, 1963, 1967; McCallum et al., 1971) and antimony trisulfide (Brieger et al., 1954). These studies are summarized in Table 3-2. Watt (1980, 1981, 1983) and ASARCO Inc. (1980) all report portions of the results from apparently the same study. In this study 148 female CDF rats were divided into three groups (numbers per group not specified). Animals were exposed to antimony trioxide dust at levels of 1.6 ± 1.5 mg/m³ or 4.2 ± 3.2 mg/m³ (as antimony), 6 hours/day, 5 days/week for 1 year. At baseline and following 3 months, 6 months and 1 year of exposure hematology, serum enzymes and serum chemistries (endpoints not otherwise specified) were evaluated. Body and organ weights were evaluated and "selected" tissues were examined histopathologically.

TABLE 3-2

Summary Table for Chronic Toxicity of Antimony and Compounds

Route	Compound	Species/ Strain	Sex	No. at Start	Vehicle	Exposure or Dose	Response	Reference
Oral	potassium antimony tartrate	rat/Long-Evans	M,F	50/sex	drinking water	5 ppm antimony for the lifetime	Decreased longevity, altered serum biochemistries	Schroeder et al., 1970
	potassium antimony tartrate	mice/ Swiss	M,F	54/sex	drinking water	5 ppm antimony for the lifetime	Decreased longevity in female mice	Kanisawa and Schroeder, 1969
Inhalation	antimony trioxide	human/NA	NR	NR	dust	>0.5 mg/m³, 40 hours/week, 5-35 years	Dermatitis and pneumoconiosis with no apparent symptoms	McCallum, 1963, 1967; McCallum et al., 1971
	antimony trisulfide	human/NA	NR	75	dust	0.58-5.5 mg/m³, 40 hours/week for 24 months	Altered ECG patterns	Brieger et al., 1954

NR = Not reported; NA = not applicable

Suggestive elevations in BUN were seen; however, values were only statistically different from controls in males after 6 months, but not 1 year of exposure. Lung weights showed a "consistent pattern" of being heavier in exposed rats in a dose-related manner. Apparently interim sacrifices were conducted, although numbers of animals sacrificed are not specified. The text states that the high-dose rats had statistically increased lung weights at the 9- and 12-month time points.

The primary findings at autopsy were both nonneoplastic and neoplastic lung lesions. The nonneoplastic lesions were described as focal fibrosis, adenamatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumonocyte hyperplasia and pigmented macrophages.

Neoplastic changes in the lungs were seen in animals 18 months of age or older with the majority seen in animals surviving 29 months. Apparently, postexposure observations were conducted since exposure only lasted 1 year. An unexplained figure suggests postexposure sacrifices ~10 weeks and ~48 weeks postexposure (Watt, 1981). Lung neoplasms in general appeared to arise from the alveolar epithelial lining. Tumor incidences were reported for six sacrifice times that appear to be 20, 33 and 53 weeks after the start of exposure and 10 and 48 weeks postexposure. For all lung neoplasms combined incidences were significantly elevated in groups sacrificed at 10 weeks and at 53 weeks postexposure. The author states that there were significant differences in both the low- and high-dose groups; however, this statement is perplexing. At 10 weeks postexposure incidences were 1/6, 0/5 and 5/7 for the control, low- and high-dose groups, respectively. After 53 weeks these same groups showed incidences of 1/13, 1/17 and 14/18. The predominant tumor type was scirrhous carcinoma, which was reported at an incidence of 5/7 and 9/18 for the high-dose group at 10 and 53 weeks, respectively, while the control and low-dose incidence was zero.

This study is difficult to evaluate because of the fragmented reporting. In addition, there was apparently quite a lot of variability in exposure concentrations.

An additional unpublished study (Wong et al., 1979; EPL, 1981) reported the results of an inhalation study in which rats were exposed to "50±40 mg/m³" antimony trioxide for 1 year (7 hours/day, 5 days/week) and then held for 1 year. Neoplastic lesions were found in female rats but not males. No further details were provided.

The lung and heart appear to be target organs for the toxic effects of antimony compounds in humans. McCallum (1963, 1967) and McCallum et al. (1971) observed dermatitis and pneumoconiosis with no overt symptoms in workers exposed to concentrations >0.5 mg/m³ antimony trioxide, 40 hours/week for 5-35 years (see Table 3-1). Brieger et al. (1954) observed altered ECG patterns in workers exposed to 0.58-5.5 mg/m³ antimony trisulfide for 2 years.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Limited data concerning the teratogenic and reproductive effects of antimony compounds were available. Rabbits given high oral doses (15-55 mg every other day for 30-90 days) of metallic antimony had frequent abortions (Boveri, n.d.). James et al. (1966) fed four yearling ewes a dose of 2 mg/kg bw antimony potassium tartrate for 45 days or throughout gestation, and offspring of treated ewes were normal.

3.3.2. Inhalation. Belyaeva (1967) compared women working in an antimony metallurgical plant with a similar group of women not exposed to antimony. The exposed group had higher incidences of spontaneous abortions (12.5 vs. 4.1%), premature births (3.4 vs. 1.2%) and gynecological problems (77.5 vs. 56%). The gynecological problems included menstrual cycle disorders (61.2

vs. 35.7%), inflammatory disease (30.4 vs. 55.3%) and other reproductive problems (8.4% of exposed women). These women were exposed to unspecified amounts of antimony trioxide, metallic antimony and antimony pentasulfides. Children born to these exposed women weighed significantly less after 1 year when compared with children born to nonexposed women; there were no statistically significant differences in weights at birth of the two sets of children.

Aiello (1955) observed a higher rate of premature deliveries and frequent dysmenorrhea among female workers engaged in antimony smelting and processing (U.S. EPA, 1980a).

Belyaeva (1967) exposed 24 female rats repeatedly to antimony trioxide dust by inhalation for 1.5-2 months at doses of 250 mg/m^3 for 4 hours/day (NIOSH, 1978). Rats were treated in this manner 3-5 days before estrus and then mated. Exposure to the dust was continued until 3-5 days before delivery. Of the treated rats, 16/24 conceived whereas all of the 10 control rats became pregnant. Average litter sizes for treated rats were 6.2 and for control rats 8.3. No morphological changes were seen in the fetuses. Resorption and fetal deaths were not discussed.

3.4. TOXICANT INTERACTIONS

Information concerning toxicant interactions could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Data concerning the carcinogenicity of antimony by the oral route could not be located in the available literature.

4.1.2. Inhalation. Davies (1973) conducted a retrospective epidemiological study in 1081 male and female antimony process workers. Of the 56 deaths reported for this cohort, 10 were attributed to lung cancer, and 9 of these deaths occurred in workers engaged in antimony smelting and related activities. The number of deaths expected was 5.7, based on community death rates, yielding a relative risk of 1.75. Statistical analysis of these data were not reported. Unfortunately, this study has only been reported in a short letter making a critical analysis of the results unfeasible. Additional epidemiological studies are in progress (U.S. EPA, 1983f). The available data are considered to be suggestive, but inadequate to draw firm conclusions.

4.2. BIOASSAYS

4.2.1. Oral. Schroeder et al. (1970) and Kanisawa and Schroeder (1969) gave rats and mice (see Section 3.2.1.) 5 ppm antimony as potassium antimony tartrate in drinking water over the lifespan and observed no carcinogenic effect. Tumors were located by gross inspection at necropsy. Histopathological examination was performed only on grossly identified tumors, grossly observed lesions and sections of heart, lung, liver, kidney and spleen. Decreased longevity was observed in rats of both sexes and in female mice, but the investigators did not feel that shortened lifespan altered the expression of the carcinogenicity of antimony. The authors felt that antimony did not exhibit carcinogenic activity. This study was an inadequate test of carcinogenicity for a number of reasons including: 1) only one dose

level was employed; 2) no evidence was presented to indicate the MTD was approached; and 3) inadequate histopathological evaluations were conducted.

4.2.2. Inhalation. A statistically significant increase in lung tumors (Table 4-1) was observed in female rats exposed to 4.2 mg/m³ antimony from antimony trioxide for 6 hours/day, 5 days/week for 1 year (ASARCO, Inc., 1980; Watt, 1980, 1981, 1983). A statistically significant increase in lung tumors was not observed in female rats exposed to 1.6 mg/m³ antimony. Watt (1983) further reported that S-1 miniature swine exposed by the same exposure schedule did not develop exposure-related alterations.

Wong et al. (1979) exposed male and female rats to 50 or 40 mg/m³ antimony trioxide or 50 or 40 mg/m³ antimony trisulfide for 7 hours/day, 5 days/week for 1 year followed by a 1-year observation period. Neoplastic lesions developed in female rats exposed to either compound; nonneoplastic lesions developed in males.

U.S. EPA (1983e) stated that the Watt (1980, 1981, 1983) and Wong et al. (1979) studies provided qualitative evidence of oncogenic effects in rats, but found these studies inadequate for quantitative risk assessment because only one sex was used in the Watt (1980, 1981, 1983) studies and only one exposure level was used by Wong et al. (1979). No data exists concerning the carcinogenicity of metallic antimony. Since metallic antimony is oxidized to antimony trioxide during processing, there would be no significant differences in the consequences of exposure to the two substances, and the oncogenic risk of exposure to metallic antimony should be "generally equivalent" to exposure to antimony trioxide (U.S. EPA, 1983f). Antimony potassium tartrate has been scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1986) and is currently being assigned to a laboratory for toxicology study.

TABLE 4-1

Tumor Incidence in Female Rats Exposed by Inhalation to Antimony Trioxide[a,b]

Exposure[c]/Dose (mg/kg/day)[d]	Duration of Treatment (days)	Duration of Study (days)	Target Organ	Tumor Type	Tumor Incidence
4.2 mg/m³ (0.48 mg/kg/day)	365	730	lung	carcinoma adenoma	15/17
1.6 mg/m³ (0.18 mg/kg/day)	365	730	lung	carcinoma adenoma	1/17
0	NA	730	lung	carcinoma adenoma	1/13

[a]Source: ASARCO, Inc., 1980; Watt, 1981, 1983

[b]Purity of compound not reported

[c]Exposures were for 6 hours/day, 5 days/week

[d]Calculated by assuming a respiratory rate of 0.223 m³/day and a reference body weight for rats of 0.35 kg, and expanding to continuous exposure.

NA = Not applicable

4.3. OTHER RELEVANT DATA

Kanematsu et al. (1980) observed positive mutagenic effects of antimony trioxide in the recombinant DNA Bacillus subtilis assay, indicating that antimony trioxide damages DNA (U.S. EPA, 1979). Antimony trioxide was negative for reverse mutation in Salmonella typhimurium strains TA1535, TA100, TA98, TA1537 and TA1538 (Kanematsu et al., 1980). Antimony sodium tartrate caused chromosomal aberrations in cultured human cells (Paton and Allison, 1972). Since differences in chemical and physical properties exist between antimony tartrate and antimony oxides, the U.S. EPA does not consider these data relevant to assessing the mutagenicity of metallic antimony, antimony trioxide or antimony trisulfide (U.S. EPA, 1983f).

4.4. WEIGHT OF EVIDENCE

Some data exist regarding induction of lung tumors in female rats after inhalation exposure in a chronic study by Watt (1983), using dose levels close to the present OSHA standard. U.S. EPA (1983f) reported that none of the available studies, including Watt (1983) and Wong et al. (1979), are suitable for quantitative determination of carcinogenic risk and the mutagenicity studies are not conclusive. The deficiencies of these studies were discussed in detail in previous sections of this report; however, the deficiencies relate primarily to quantitative exposure-response estimates. These studies are considered to represent adequate qualitative evidence of carcinogenicity in experimental animals following inhalation exposure. Increased incidence of lung cancer-related mortality has been reported in workers associated with smelting operations (Davies, 1973). However, this report was limited to a 2-page letter making it impossible to adequately evaluate this study. Applying the criteria for weight of evidence proposed by EPA (U.S. EPA, 1986b), antimony is most appropriately classified in

Group B2, Possible Human Carcinogen, based on sufficient animal data. Human data, while suggestive, are considered inadequate because of reporting deficiencies. This classification will require reevaluation pending more complete reporting of existing human studies or new reports of human exposures. The B2 classification currently can be applied only to inhaled antimony. Current data are inadequate to assess the potential carcinogenicity of ingested antimony. This would result in an EPA classification of D for orally administered antimony.

U.S. EPA (1986a) derived an RfD of 0.0004 mg/kg/day for antimony based on a rat chronic oral bioassay (Schroeder et al., 1970). U.S. EPA (1980a) derived an ambient water quality criterion of 145 µg/ℓ, or 45 mg/ℓ if consumption is from fish and shellfish alone, for antimony [also based on Schroeder et al. (1970)]. U.S. EPA (1985a) derived RfDs for a 70 kg man of 29.3, 30.9 and 32.9 µg/day for antimony trioxide, tetraoxide and pentoxide, respectively, based on Schroeder et al. (1970). NAS (1980) suggested a chronic SNARL based on a LOAEL of 0.0025 mg/kg reported by Arzamastsev (1964). U.S. EPA (1985b) did not propose an RMCL for antimony because "preliminary analysis indicated limited potential for drinking water exposure causing a significant risk from these substances."

OSHA (1985) adopted a PEL of 0.5 mg/m³ for antimony and compounds. NIOSH (1978) recommended a TWA concentration limit of 0.5 mg/m³ based on exposure-associated cardiac and respiratory changes and irritation of the skin and mucous membranes. ACGIH (1986) recommended a TLV-TWA of 0.5 mg/m³ as antimony for antimony and compounds.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Subchronic oral data are not adequate for quantitative risk assessment because the available studies, with one exception, do not define thresholds for toxicity. The study by Smyth and Carpenter (1948) could be used to derive an RfD_{SO}, however, but it was considered inadequate because small numbers of animals were tested and no controls were maintained. RfD_0 values for selected antimony compounds are derived in Section 6.2.1.

6.1.2. Inhalation (RfD_{SI}). Several subchronic inhalation studies were reviewed in Section 3.1.2., but these studies do not define either individually or collectively the thresholds for toxicity. The data, therefore, are insufficient for derivation of an RfD_{SI}. In addition, bioassay data suggest that antimony is carcinogenic by the inhalation route (see Section 6.2.2.).

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Many of the EPA documents on antimony and compounds have based risk assessment for individual members of a class by a particular route of exposure on the most toxic compound of the class to provide the greatest margin of safety (U.S. EPA, 1980, 1985a, 1986a). ACGIH (1986), NIOSH (1978) and OSHA (1985), however, have reported a single value when considering antimony as a class. Observations from a limited database indicate that the target organs for the toxic effects of antimony and compounds by the oral or inhalation routes include the heart, lung, liver and kidney (see Table 3-1).

The approach to derivation of RfD_0 values taken in this document incorporates previous U.S. EPA (1980a, 1985a, 1986a) analyses. U.S. EPA (1980a) calculated an RfD for antimony from the LOAEL of 5 ppm antimony (from potassium antimony tartrate) in the drinking water of rats exposed for their lifetimes (Schroeder et al., 1970). This treatment was associated with reduced lifespan in both sexes and blood biochemistry alterations in males. U.S. EPA (1980a) assumed a water intake of 0.025 ℓ/day and estimated an average body weight for the rats of 0.3 kg (presumably based on the tabular data provided by the investigators) to compute a dose of 417 μg/kg/day. Application of an uncertainty factor of 100 resulted in an RfD of 4.17 μg/kg/day or 292 μg/day for a 70 kg human. An uncertainty factor of 100 rather than 1000 was used, because it was felt that this LOAEL "approximates the 'no-effect' level for antimony induced effects on growth and longevity."

In a more recent analysis (U.S. EPA, 1985a, 1986a), a daily dose of 350 μg/kg/day was estimated for the 5 ppm level of antimony in drinking water in the Schroeder et al. (1970) experiment with rats. Although mg/kg/day doses were not reported for this experiment, this value is consistent with consumption rates reported by these investigators for the same strain of rat and similar experimental protocols utilizing different metals (Kanisawa and Schroeder, 1969).

The more recent U.S. EPA (1985a, 1986a) analysis chooses an uncertainty factor of 1000 rather than 100, as was chosen in the earlier (U.S. EPA, 1980a) report. The choice of the larger uncertainty factor seems more appropriate when applied to a LOAEL associated with reduced longevity, regardless of effects on growth, and is, therefore, used in this analysis.

Application of an uncertainty factor of 1000 to a dose of 350 µg/kg/day results in an RfD_0 for antimony of 0.350 µg/kg/day or 0.024 mg/day (24.5 µg/day) for a 70 kg human (U.S. EPA, 1986a). By correcting for differences in molecular weights, RfD_0 values for other antimony compounds are as follows: antimony potassium tartrate, 65.4 µg/day; antimony trioxide, 29.3 µg/day; antimony tetroxide, 30.9 µg/day; antimony pentoxide, 32.5 µg/day (U.S. EPA, 1985a). RfD_0 values for more soluble salts and organic compounds of antimony are not calculated because virtually nothing is known about the subchronic or chronic toxicity of these substances.

U.S. EPA (1983b) derived an oral CS of 38 for antimony potassium tartrate based on the endpoint of decreased longevity in rats exposed to 5 ppm antimony (equivalent to 13.7 ppm of antimony potassium tartrate) in drinking water over a lifetime (Schroeder et al., 1970).

6.2.2. Inhalation (RfD_I). Qualitative evidence strongly suggests that antimony is a possible human carcinogen. A retrospective epidemiological study suggested that deaths from lung cancers increased in antimony workers (Davies, 1973). An increased incidence of lung cancers was observed in rats exposed to 4.2, but not to 1.6 mg antimony/m³, 6 hours/day, 5 days/week for 1 year and observed for another year (Watt, 1980, 1981, 1983; ASARCO, Inc., 1980). U.S. EPA (1983f) evaluated these data and determined them inadequate for quantitative assessment of carcinogenic risk. Further carcinogenicity testing was recommended. Pending the outcome of these tests, and based upon the qualitative evidence for carcinogenicity, an RfD_I is not derived.

U.S. EPA (1985a) based an inhalation CS for the antimony oxides on the Watt (1983) observation of fibrotic lung changes in female rats at a dose of 0.18 mg/kg/day, which corresponded to a chronic human MED of 2.2. An RV_d

of 5.0 was calculated, and an RV_e of 6 was assigned for the fibrotic lung changes. Multiplying the RV_d of 5 by an RV_e of 6, a CS of 30 was obtained. Watt (1983) used a 1-year exposure period in rats which arguably should be considered subchronic and the converted dose should be divided by an additional factor of 10; thus, a chronic human MED of 0.2 mg/day would be obtained, corresponding to an RV_d of 6.5. Multiplying an RV_d of 6.5 by an RV_e of 6 would result in a CS of 39.

U.S. EPA (1983a) based an inhalation CS of 46 on Brieger et al. (1954) who observed altered ECG patterns in workers exposed to concentrations of antimony trisulfide $\geq$0.58 mg/m^3 (0.2 mg/m^3 as antimony). This CS was not adopted because of lack of control data. Additionally, the workers had been exposed to mixtures of chemicals.

U.S. EPA (1983c) derived an inhalation CS of 18 for antimony trioxide. (For a discussion of the inadequacies of this value see U.S. EPA, 1985a.) The CS of 39 associated with fibrotic and hyperplastic changes in the lungs of rats exposed to antimony trioxide by inhalation for 1 year (Watt, 1980, 1981, 1983; ASARCO, Inc., 1980) is chosen as most stringently representing the toxicity of antimony.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. No data concerning the oral carcinogenicity of antimony and compounds in humans was available. Available animal studies suggested that antimony and compounds were not carcinogenic by the oral route (Schroeder et al., 1970; Kanisawa and Schroeder, 1969).

6.3.2. Inhalation. Davies (1973) suggested that occupational exposure to antimony may lead to lung cancer in humans. Davies (1973) reported that 10 deaths from lung cancer were observed in occupationally exposed workers. The expected number of deaths attributed to lung cancer was 5.7, yielding a relative risk of 1.75.

Watt (1983) observed a statistically significant increase in lung tumors (see Table 4-1) in female rats exposed to 4.2 mg/m³ antimony from antimony trioxide for 6 hours/day, 5 days/week for 1 year followed by a 1-year observation period.

Wong et al. (1979) observed lung tumors in male and female rats exposed to 50±40 mg/m³ antimony trioxide for 7 hours/day, 5 days/week for 1 year.

U.S. EPA (1983f) considered these studies inadequate for quantitative risk assessment, but stated they that provided qualitative evidence of an oncogenic effect.

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U.S. EPA (1983f) considered these studies inadequate for quantitative risk assessment, but stated they that provided qualitative evidence of an oncogenic effect.

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APPENDIX

Summary Table for Antimony and Compounds

Values	Species	Experimental Exposure/Dose	Effect	Reference Dose (RfD or RfD_S)	Reference
Inhalation					
RfD_{SI} and RfD_I (formerly AIS AND AIC, respectively	rat	1.6 mg antimony/m³ exposure to antimony trioxide, 6 hours/day, 5 days/week for 1 year followed by 1-year observation period (0.18 mg/kg/day)[a]	fibrotic changes and hyperplasia of the lungs, lung cancer	not derived because of qualitative evidence for carcinogenicity	Watt, 1980, 1981, 1983; ASARCO, Inc., 1980
Maximum CS	rat	1.6 mg antimony/m³ exposure to antimony trioxide 6 hours/day, 5 days/week for 1-year observation period (0.18 mg/kg/day)[a] (RV_d = 6.5)	fibrotic changes and hyperplasia of the lungs (RV_e = 6)	CS = 39	Watt, 1980, 1981, 1983; ASARCO, Inc., 1980
Oral					
RfD_{SO}	NA	NA	NA	ND	
RfD_O	rat	5 ppm antimony from antimony potassium tartrate in drinking water for lifetime (417 µg/kg/day)[b]	reduced lifespan in both sexes, altered blood biochemistries in males	antimony, 0.024 mg/day (24.5 µg/day); antimony potassium tartrate, 65.4 µg/day; antimony trioxide, 29.3 µg/day; antimony tetroxide, 30.9 µg/day; antimony pentoxide, 32.5 µg/day.	Schroeder et al., 1970

[a]Expanded to continuous exposure and assuming an inhalation rate of 0.223 m³/day and a body weight of 0.35 kg for rats.

[b]Transformed dose estimated by U.S. EPA, 1980a