United States
Environmental Protection
Agency

EPA/690/R-08/020F
Final
7-29-2008

Provisional Peer Reviewed Toxicity Values for

Soluble Antimony Compounds
(Various CASRNs)

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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR SOLUBLE ANTIMONY COMPOUNDS (VARIOUS CASRNs)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically

updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

There are many forms of antimony that exist in the environment. The primary water soluble antimony compounds with available toxicology data include antimony potassium tartrate, antimony trichloride, and antimony trisulfide (ATSDR, 1992). IRIS records provide an oral RfD for antimony (CASRN 7440-36-0) based on a chronic drinking water study with potassium antimony tartrate (U.S. EPA, 2007). The chronic oral RfD of 4E-4 mg/kg-day for antimony (Sb) is based on a LOAEL of 0.35 mg Sb/kg-day for reduced life span and serum chemistry changes in male and female rats exposed to potassium antimony tartrate in drinking water for 2 years by Schroeder et al. (1970). A composite uncertainty factor (UF) of 1000 was applied in derivation of the RfD (UFs of 10 each to account for the LOAEL to NOAEL conversion, interspecies extrapolation, and interindividual differences). The RfD of 4E-4 mg/kg-day is included in the Drinking Water Standard and Health Advisories List (U.S. EPA, 2006). A 1980 Ambient Water Quality Criteria Document (AWQCD) (U.S. EPA, 1980) and a 1985 Health Effects and Environmental Profile (HEEP) for Antimony Oxides (U.S. EPA, 1985) are listed as the source documents for the IRIS RfD, which was verified on November 6, 1985. The HEAST (U.S. EPA, 1997) refers to IRIS for the chronic RfD and adopts the chronic RfD as a conservative estimate of the subchronic RfD. The HEAST (U.S. EPA, 1997) also includes separate chronic and subchronic oral RfD values of 9E-4 mg/kg-day for antimony potassium tartrate calculated by analogy to antimony by correcting for differences in molecular weight, citing the HEEP for Antimony Oxides (U.S. EPA, 1985) and a Health Effects Assessment (HEA) for Antimony and Compounds (U.S. EPA, 1987). No other relevant EPA documents were located in the CARA lists (U.S. EPA, 1991, 1994).

IRIS (U.S. EPA, 2007) includes an RfC for antimony trioxide, but no RfC for soluble antimony compounds. The Agency for Toxic Substances and Disease Registry (ATSDR) has prepared a toxicological profile for antimony (ATSDR, 1992), but did not derive oral or inhalation MRL values. ATSDR concluded that reduced lifespan in the Schroeder et al. (1970) study was not an appropriate basis for a chronic MRL and noted that subchronic oral studies did not examine sensitive endpoints of myocardial damage (i.e., altered EKG), which is suggested to be a critical endpoint by subchronic inhalation studies of antimony trisulfide.

A cancer assessment for antimony is not available on IRIS (U.S. EPA, 2007) or in the HEAST (U.S. EPA, 1997). The HEEP (U.S. EPA, 1985) and HEA (U.S. EPA, 1987) acknowledged there was suggestive evidence of lung cancer in female rats exposed to antimony trioxide by inhalation, but declined to perform quantitative carcinogenicity assessments. In both cases, the decision was based on EPA's Federal Register response to an Interagency Testing Committee (ITC) recommendation for carcinogenicity testing of antimony (U.S. EPA, 1983) in which the data available at the time were characterized as inadequate to reasonably predict oncogenic risk in exposed humans. There is no evidence of lung cancer associated with other forms of antimony. U.S. EPA (1992) assigned antimony in drinking water to weight-of-evidence Group D (not classifiable as to human carcinogenicity) based on the reasoning that evidence of lung cancer following inhalation exposure to antimony trioxide is of uncertain relevance to oral drinking water exposure to antimony. Antimony is classified as Group D in the Drinking Water Standard and Health Advisories List (U.S. EPA, 2006). The International Agency for Research on Cancer (IARC) (1989) concluded that antimony trioxide is possibly carcinogenic to humans (Group 2B), based on sufficient evidence in animals and inadequate evidence in humans. IARC concluded that antimony trisulfide is not classifiable as to its carcinogenicity in humans (Group 3) due to only limited evidence for carcinogenicity in animals and inadequate evidence in humans. ACGIH (2005) classified "antimony trioxide production" as a suspected human carcinogen (Group A2), although "antimony and compounds" was not similarly classified. In the time since these assessments were performed, additional studies in both humans and animals have entered the literature. The available data regarding the carcinogenicity of antimony are reviewed below.

Computer searches of TOXLINE (1990-1997), CANCERLINE (1990-1997), DART (1989-1996), ETICBACK (1989-1996), TSCATS, CCRIS, EMIC and EMICBACK were conducted in June 1996 and May 1997 for antimony and compounds. Update literature searches were performed in January 1999 for the 1996 to 1999 time period in HSDB, RTECS, MEDLINE and TOXLINE (and its subfiles) databases. A recent update literature search was performed in January 2006 for the time period of 1999 to present in TOXLINE, MEDLINE (plus PubMed cancer subset), BIOSIS and DART/ETICBACK. Databases searched without date limitations included TSCATS, RTECS, GENETOX, HSDB and CCRIS. Search of Current Contents encompassed July 2005 to January 2006. The literature search was updated to July 2008.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure. No data were located regarding the oral toxicity or carcinogenicity of soluble antimony compounds in humans.

Inhalation Exposure. Several occupational exposure studies have examined the inhalation toxicity of antimony compounds. Most of these studies characterize the effects of exposure to antimony trioxide and other insoluble antimony compounds (e.g., metallic antimony, antimony ore, antimony pentoxide). These studies are described in a separate provisional toxicity value report for antimony trioxide. One study was available that described the effects of inhalation exposure to antimony trisulfide in occupational workers (Brieger et al., 1954). Antimony trisulfide is a water soluble antimony compound and a summary of this study is provided below.

Brieger et al. (1954) examined 113 factory workers exposed to antimony trisulfide for 8 months to 2 years. Air concentrations of antimony trisulfide ranged from 0.58 to 5.5 mg/m^3, with the majority over 3.0 mg/m^3; the particle size was not reported. The workers also may have been exposed to phenol formaldehyde. Blood pressure readings above 150/90 were observed in 14 of the workers; 24 workers had blood pressure readings under 110/70. Altered EKG readings (mostly of the T-waves) were observed in 37 out of 75 of the workers. EKG changes were detected in 12 out of 56 workers reexamined after antimony trisulfide use was discontinued. A large number of workers complained of gastrointestinal disturbances (details not provided). Gastrointestinal ulcers were detected in 7 out of the 111 workers examined (63 per 1000) as compared to the incidence for the total plant population (59/3912, 15 per 1000). Respiratory irritation was not reported.

Animal Studies

Oral Exposure. Repeated-dose oral exposure studies in animals have been conducted using potassium antimony tartrate (Omura et al., 2002; Poon et al., 1998; NTP, 1992; Schroeder et al., 1970; Schroeder et al., 1968; Kanisawa and Schroeder, 1969) and antimony trichloride (Marmo et al., 1987; Rossi et al., 1987; Angrisani et al., 1988).

Omura et al. (2002)

The testicular toxicity of antimony was evaluated in Crj:Wistar rats (7-8/group) and Cjr:CD-1 mice (8-10/group) (Omura et al., 2002). Antimony potassium tartrate (purity > 99.5%) (27.4 mg/kg-day or 10 mg Sb/kg-day) was administered by oral gavage to rats (3 days/week for 4 weeks) and mice (5 days/week for 4 weeks). Animals were sacrificed by carbon dioxide inhalation 24 hours after the final gavage dose was administered. The testes, epididymides, ventral prostate and seminal vesicle (without fluid) were removed and weighed. Histopathological changes were evaluated in the testes and the number, motility and morphology of sperm from the cauda epididymides were assessed. One control mouse died due to gavage error. No significant effect on body weight or organ weight of reproductive tissues was observed. Sperm parameters were not affected by antimony treatment and histopathology results were essentially negative. A NOAEL value of 10 mg Sb/kg-day was derived for male

reproductive effects in this study; a LOAEL value was not available (no effects were seen at the highest dose tested).

Poon et al. (1998)

Sprague-Dawley rats (15/sex/group) were exposed to 0, 0.5, 5.0, 50 or 500 ppm antimony potassium tartrate (99.95% pure) in the drinking water for 90 days (Poon et al., 1998). An additional 10 rats/sex were included in the control and high-dose groups and these animals were given tap water for a 4-week recovery period following exposure. Clinical signs were monitored daily; body weights and food and water consumption were measured weekly. At the end of the 90-day exposure period, 50% of the animals were placed in metabolic cages to provide an overnight urine sample. All animals were anaesthetized and exsanguinated via the abdominal aorta to provide blood samples for routine hematology and clinical chemistry. Serum was also analyzed for thyroxine (T4), thyroid hormone binding ratio, and thiobarbituric acid-reactive substances (TBARS). At necropsy, the brain, thymus, heart, kidney, spleen and liver were excised and weighed and the concentration of antimony was measured in these organs. The concentration of antimony was also measured in a sample of abdominal fat, red blood cells (RBCs) and serum. The following tissues and organs were processed for histopathological examination: brain, pituitary, thyroid, trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, esophagus, gastric cardia, fundus and pylorus, duodenum, jejunum, ileum, cecum, colon, urinary bladder, skin, bone marrow and gonadal tissues. Liver homogenates were prepared and the specific activities of aniline hydroxylase, aminopyrine N-demethylase, ethoxyresorufin-O-deethylase (EROD) and UDP-glucuronosyltransferase were measured using 10,000 x g supernatants.

No clinical signs were evident in rats exposed to antimony potassium tartrate. In high-dose rats (500 ppm, both sexes), there were observed reductions in water consumption (-35%), food consumption (-12%) and body weight gain (% change not indicated). These parameters rapidly returned to control levels during the 4-week recovery period. Based on the body weight and drinking water consumption data, the authors calculated average daily antimony potassium tartrate doses of 0, 0.06, 0.56, 5.58 or 42.17 mg/kg-day for male rats and 0, 0.06, 0.64, 6.13 or 45.69 mg/kg-day for female rats. These doses correspond to 0, 0.024, 0.22, 2.2 or 17 mg Sb/kg-day for male rats and 0, 0.024, 0.25, 2.4 or 18 mg Sb/kg-day for female rats. Dose-dependent increases were evident in tissue antimony concentrations in the spleen, liver, kidney, brain, fat and serum, with the highest specific concentrations observed in the RBCs.

Among hematological parameters, high-dose males displayed a significant reduction in the number of platelets (-12%) and RBCs (-5%) and a slight increase in mean corpuscular volume (MCV) (+3%). The study authors suggest that this mild anemia may be related to hematuria that was observed in 3 high dose male rats. High-dose females had an increased monocyte count (+48%). Several changes were noted in clinical chemistry parameters. In female rats, there was a dose-related reduction in serum glucose concentration at concentrations of 5 ppm antimony and above (18% decrease at 500 ppm). The study authors suggest that this may be related to an inhibition of phosphofructokinase, although the clinical relevance of this change is not known. In high-dose female rats, the serum concentrations of creatinine, protein and cholesterol were reduced by 11%, 7% and 24%, respectively and alkaline phosphatase activity was decreased by 13%. A 12 to 14% increase in the thyroid hormone binding ratio was

observed in female rats that drank water containing 50 or 500 ppm antimony. Creatinine concentration and alkaline phosphatase activity were also reduced in high-dose male rats (10 and 41%, respectively). All clinical chemistry parameters were similar to control values by the end of the 4-week recovery period. No treatment-related changes were observed in serum sorbitol dehydrogenase, aspartate aminotransferase, creatinine kinase, thyroxin, or TBARS. No dose-related changes were observed in hepatic mixed-function oxidase enzyme activities, with the exception of ethoxyresorufin-O-deethylase, which was increased by 55% in high-dose male rats. Glutathione transferase activity was increased in high-dose male (11%) and female (18%) rats.

Few gross lesions were evident at necropsy. A single male in the high-dose group had a cirrhotic liver and one female in the 0.5 ppm group had a nodular, fibrotic spleen. Female rats in the 50 ppm dose group had a lower thymus to body weight ratio than control rats (22% decrease) and male and female rats from the high-dose groups had increased kidney-to-body-weight ratios (8% increase for males, 18% increase for females). No other organ weight changes were noted. Histopathological changes were observed in the thyroid and liver, with lesser changes seen in the thymus, spleen and pituitary gland. Thyroid effects included reduced follicle size, increased epithelial height and nuclear vesiculation. Anisokaryosis and nuclear hyperchromicity were observed in the liver. Increased portal density and increased perivenous homogeneity were also noted in the cytoplasm of hepatocytes. Other observations included reduced cortical volume and increased medullary volume in the thymus, sinus congestion in the spleen and cytoplasmic vacuolation and inclusions in the pituitary gland. The study authors concluded that all histological findings were mild adaptive changes and did not represent significant target organ toxicity. Thyroid and liver lesions were found in control rats. The incidence and severity of these lesions was generally increased in treated groups; however a clear dose-response relationship was not apparent for many endpoints. An adjusted NOAEL of 18 mg Sb/kg-day was derived from this study, because histological changes were considered adaptive in nature and hematology and clinical chemistry findings were not indicative of significant toxicity. A LOAEL value was not provided by this study (no adverse effects were seen at the highest dose tested).

NTP (1992)

A 14-day drinking water study using antimony potassium tartrate (purity >99.4%) was performed in F344 rats and B6C3F1 mice (5/sex/group) (NTP, 1992). The daily antimony potassium tartrate doses calculated by the study authors were 0, 16, 28, 59, 94 or 168 mg/kg-day in rats and 0, 59, 98, 174, 273 or 407 mg/kg-day in mice. These doses correspond to 0, 6, 11, 24, 38 or 67 mg Sb/kg-day in rats and 0, 24, 39, 70, 109 or 163 mg Sb/kg-day in mice. Animals were observed twice per day. Body weights were measured on days 1, 8 and prior to sacrifice on day 15, and water consumption was measured on day 7 or 8 and on day 15. Following sacrifice by CO_2 inhalation, the liver, thymus, right kidney, right testis, spleen, heart, brain and lungs were removed, weighed and evaluated for histopathology. The tissue concentration of antimony was measured in the blood, kidney, heart, liver and spleen.

Water consumption was decreased 20 to 30% in male rats receiving 38 and 67 mg Sb/kg-day and 10-40% in female rats receiving doses greater than 11 mg Sb/kg-day. No clinical signs of toxicity or significant changes in body weight were observed in rats. Relative liver weight was increased in male and female rats for the highest dose group (67 mg Sb/kg-day) and relative

kidney weight was increased in female rats from this group. No histopathological changes were observed in rats, with the exception of prominent staining of protein droplets observed in the cytoplasm of renal tubule cells of male rats. Antimony concentrations were detected in the kidney, heart, spleen and liver of rats, but were highest in blood (15 to 20 μg/kg). A NOAEL of 67 mg Sb/kg-day was derived for rats in this study based on the lack of histopathological effects. A LOAEL dose was not determined from this study.

Body weight was significantly decreased in male mice at doses of 109 mg Sb/kg-day (7% decrease) and 163 mg Sb/kg-day (25% decrease) and in female mice in the 163 mg Sb/kg-day dose group (18% decrease) at 8 days of exposure. Body weight values recovered and were similar to controls at the end of the study (day 16) for all dose groups except high-dose males (7% decrease on day 16). One female mouse from the high-dose group died during the study. Water consumption was decreased in all treatment groups. Clinical signs of toxicity were observed (i.e., rough haircoat, emaciation, abnormal posture, hypoactivity and decreased fecal material consistent with water avoidance); however, the study report did not specify the dose groups in which these signs were seen. Dose-related increases were observed in relative liver weight (not further described). Liver and forestomach lesions were observed in male and female mice from the high-dose group (incidence values were not provided). Gross lesions described as small, white nodules, were observed in the forestomach of three male mice and one female mouse. Histopathology revealed that these nodules consisted of focal areas of ulceration and necrosis, with inflammation of the squamous mucosa extending to the muscularis of the forestomach. Focal hyperplasia of the squamous epithelium of the forestomach was also observed. Cytoplasmic vacuolization was observed in hepatocytes from all male and female mice in the high-dose group. Centrilobular hepatocytes were slightly enlarged and showed cytoplasmic staining; however, nuclear displacement was not observed. NOAEL and LOAEL values could not be clearly determined from the mouse data in this study. Body weight decreases and histopathological changes in the forestomach and liver were observed at the highest dose; however, it is not clear whether clinical signs of toxicity were also evident in lower dose groups.

Schroeder et al. (1970)

Schroeder et al. (1970) exposed groups of 51-52 male and 54-59 female Long-Evans rats to 0 or 5 μg/mL of antimony as potassium antimony tartrate in the drinking water from weaning through natural death (up to 45 months in this study). Rats were weighed periodically throughout the study. Upon death, animals were necropsied and grossly visible tumors and other lesions were described. An outbreak of pneumonia during this study led to the deaths of 9 treated males, 3 treated females, 19 control males and 12 control females. Survival curves were corrected to take this non-treatment related mortality into account. Survival (corrected for pneumonia mortality) of antimony-exposed rats was reduced after 12 months in males and after 21 months in females compared to untreated controls. Median life span was reduced over 100 days in both males and females, and longevity (defined as the mean age of the last surviving 10%) was significantly reduced in both sexes as well. Body weights (reported only for the first 18 months of the study) did not differ from controls. Heart weight was reduced by 19% in treated male rats, as compared to control values. Heart weight was similar to controls for females rats exposed to potassium antimony tartrate. The non-fasting serum glucose concentration was decreased by 28% in treated male rats and 30% in treated female rats, as

compared to controls. Serum cholesterol was increased in treated male rats (+26%) and decreased in treated female rats (-16%), compared to serum cholesterol concentrations in control rats. The incidence of grossly visible tumors at necropsy was not affected by antimony exposure in male or female rats. The chronic oral RfD of 4E-4 mg/kg-day for antimony was calculated from a LOAEL of 0.35 mg Sb/kg-day, a dose reported in IRIS to be associated with the 5 ppm antimony concentration in drinking water (U.S. EPA, 2007).

Schroeder et al. (1968); Kanisawa and Schroeder (1969)

These researchers conducted a similar study in mice (Schroeder et al., 1968; Kanisawa and Schroeder, 1969). Groups of 54-55 male and 54 female Charles River CD mice were given 0 or 5 μg/mL of antimony as the potassium tartrate in the drinking water from weaning through natural death (up to 33 months in this study). The researchers estimated the antimony dose as 0.35 mg Sb/kg-day (5 μg/mL x 7 mL/d/0.1 kg). The mice were weighed periodically and observed for mortality. Dead animals were necropsied and examined for grossly visible tumors and other lesions, which were sectioned, stained and examined by light microscopy. Survival (%) of male and female mice exposed to antimony was similar to survival of controls throughout the study. The median life span of exposed female mice was reduced by 49 days compared to controls, but longevity (mean age of the last surviving 10%) was not affected. Body weights were reduced significantly compared to controls after 6 months in female mice and after 18 months in male mice. Exposure to antimony had no effect on the incidence or type of tumors detected by gross necropsy in male or female mice. These studies were of limited utility for the evaluation of cancer effects due to use of a single dose level, failure to consider whether the dose used approached the maximum tolerated dose (MTD), and reliance on gross necropsy for detection of tumors (i.e., failure to perform thorough histopathological examination of test animals). The LOAEL dose of 0.35 mg Sb/kg-day for antimony potassium tartrate was based on decreased body weights in female mice. A NOAEL was not available for this study.

Marmo et al. (1987); Rossi et al. (1987); Angrisani et al. (1988)

Marmo and associates (Marmo et al., 1987; Rossi et al., 1987; Angrisani et al., 1988) studied the effects of prenatal and/or postnatal exposure to antimony trichloride on vasomotor reactivity in the developing NOS albino rat. Pregnant rats (30/group) were exposed to 0, 1 or 10 mg/L antimony trichloride in drinking water from the first day of pregnancy until weaning of the offspring (22 days old) or during the postnatal period only (birth to 22 days old) (Marmo et al., 1987). Pups were randomized within 12 hours of birth and distributed to lactating dams with a litter size culled to 10 (equal numbers of male and female pups, if possible). Rat offspring were exposed to antimony trichloride in their drinking water (0, 1 or 10 mg/L) from weaning until 30 or 60 days of age. Rat offspring (10/group, 30 or 60 days old) were anesthetized and the right femoral vein was cannulated for injection of drugs. Arterial blood pressure was measured using a catheter connected to the right common carotid artery. This study measured systolic blood pressure and the response to either pressor or hypotensive agents or conditions in 30 or 60-day old offspring. The pressor response was evaluated using a 40-second occlusion of the left common carotid artery or intravenous (i.v.) injection of norepinephrine (0.1, 1, or 5 μg/kg for 5 seconds). The hypotensive response was measured after injection of isoprenaline (0.01, 0.1, or 1 μg/kg i.v. for 5 seconds) or acetylcholine (0.01, 0.1, or 1 μg/kg i.v. for 5 seconds).

Exposure to antimony trichloride (prenatal/postnatal or postnatal only) did not affect offspring arterial blood pressure, measured at 30 or 60 days after birth (Marmo et al., 1987). Combined prenatal and postnatal exposure to antimony trichloride did not affect the pressor response to carotid artery occlusion. Antimony trichloride decreased the pressor response to norepinephrine and the hypotensive response to isoprenaline at both dose levels in 60-day old rats. The hypotensive response to acetylcholine was decreased at the highest dose of antimony trichloride in 60-day old rats, while the response of the low dose group was similar to controls. No change in pressor or hypotensive responses was seen in 30-day old rats treated with antimony trichloride during the prenatal and postnatal exposure periods. In rats exposed only during the lactation period (postnatal dosing in dams) and in the drinking water after weaning, 60-day old offspring from the high-dose group showed a decrease in pressor responses to carotid artery occlusion and norepinephrine injection and a decrease in hypotensive response to isoprenaline and acetylcholine. A decreased hypotensive response to isoprenaline and acetylcholine was also seen in 30-day old offspring exposed to the highest dose of antimony trichloride. In the low-dose group (postnatal exposure), a decreased response to norepinephrine and isoprenaline was observed in 60-day old rats, while 30-day old rats were similar to controls. This study suggests that vasomotor reactivity was affected by both prenatal and postnatal exposure to antimony trichloride. However, blood pressure responses were only measured in 10 pups/dose group and the report did not indicate whether each pup came from a different litter within that dose group or whether some pups came from the same litter.

Rossi et al. (1987) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for the combined prenatal and postnatal exposure to antimony trichloride described in Marmo et al. (1987). As described above, pregnant female NOS albino rats (30 rats/group) received antimony trichloride in their drinking water (0, 1 or 10 mg/L) from gestational day 1 through weaning. Rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) were exposed prenatally and postnatally (through lactation until weaning and in their drinking water from 22 to 60 days old at concentrations of 0, 1 or 10 mg/L). The systolic arterial blood pressure of dams was measured daily for the first 20 days of gestation using a blood pressure recorder on the tail radix of conscious dams. The measurement of vasomotor reactivity in pups was described in Marmo et al. (1987) (see above). Maternal body weights were recorded on days 10 and 20 of gestation and pup body weights were measured on postnatal days 5, 10, 22, 30, and 60. The length of gestation and the number of pups/litter was recorded.

No significant alterations in litter size or macroscopic effects were observed in the offspring of dams exposed to antimony trichloride during gestation and lactation. Maternal body weight was decreased by 8% (low-dose group) to 10% (high-dose group) on the 20th day of gestation as compared to controls (statistically significant at both doses). It should be noted, however, that basal maternal body weights for each treatment group on day 0 of gestation prior to exposure were approximately 7% lower than the control group. Thus, the 8 to 10% deficit from controls seen on gestation day 20 represents a relatively small change from the 7% deficit at the start of gestation. Pup body weights were similar to controls at birth and at 5 days of age, but were decreased in the high-dose group from the 10th (24% decrease from controls) to the 60th (11% decrease from controls) day of age. Exposure to antimony trichloride did not affect

maternal or pup systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987) and are described above.

Angrisani et al. (1988) reported additional findings (i.e., maternal blood pressure and maternal and pup body weights) for postnatal (only) exposure to antimony trichloride (0, 1 or 10 mg/L) in pregnant female NOS albino rats (30 rats/group, exposed from delivery through weaning) and in rat offspring (randomized, distributed to lactating dams and culled to 10/litter with equal sex ratio) exposed postnatally (through lactation until weaning and in the drinking water from 22 to 60 days old at concentrations of 0, 1, or 10 mg/L). The systolic arterial blood pressure of dams was measured on postnatal days 1, 22, and 60 using a blood pressure recorder on the tail radix of conscious dams. The measurement of vasomotor reactivity in pups was described in Marmo et al. (1987) (see above). Maternal body weights were recorded daily until 60 days after birth and pup body weights were measured daily between postnatal days 5 and 60. Postnatal exposure to antimony trichloride did not affect maternal or pup body weights or systolic arterial blood pressure. The results of the vasomotor reactivity studies in offspring were reported by Marmo et al. (1987) and are described above.

In summary, exposure of dams and pups to antimony trichloride (prenatal and/or postnatal) did not change the systolic arterial blood pressure in dams during gestation or after birth, or in pups at 30 and 60 days of age (Marmo et al., 1987; Rossi et al., 1987; Angrisani et al., 1988). The vasomotor response to injection of pressor or hypotensive agents was decreased at both concentrations in 60-day old rats exposed prenatally and/or postnatally; however the clinical significance of the reported changes is unclear and was not discussed by the study authors (Marmo et al., 1987; Rossi et al., 1987; Angrisani et al., 1988). Combined prenatal and postnatal exposure to antimony trichloride produced a small decrease in maternal body weight during gestation (Rossi et al., 1987), while postnatal exposure during lactation did not affect maternal body weight (Angrisani et al., 1988). Pup body weights were significantly lower than controls starting at 10 days of age (24% decrease) and continuing through 60 days of age (11% decrease) following combined prenatal and postnatal exposure to 10 mg/L antimony trichoride (Rossi et al., 1987), but were not decreased by postnatal exposure only (Angrisani et al., 1988). The relationship between decreased pup and dam body weights is unclear. Both maternal and pup body weights were decreased in rats treated pre- and postnatally, but not in rats treated only postnatally. This suggests that the effect in pups may be secondary to the effect in dams even though pup body weights did not differ from controls until 10 days after birth.

Maternal doses for the gestational exposure period can be calculated using the average maternal body weight during gestation (298 g; Rossi et al., 1987) and the drinking water ingestion rate, calculated using the allometric relationship between drinking water ingestion and body weight (0.041 L/day) (U.S. EPA, 1988). The gestational maternal doses were estimated to be 0, 0.14, or 1.4 mg/kg-day antimony trichloride, or 0, 0.075, or 0.75 mg Sb/kg-day. The maternal dose of 0.75 mg Sb/kg-day was considered the LOAEL for this study, based on decreased maternal and pup body weights. The low dose of 0.075 mg Sb/kg-day was considered a NOAEL due to the very slight effect on maternal body weight and absence of effect on pup body weight at this dose.

Inhalation Exposure. Most of the subchronic and chronic animal data on the toxicity of inhaled antimony are from studies in which rats were exposed to antimony trioxide or other insoluble forms of antimony (i.e., antimony ore). These studies are described in a separate provisional toxicity value report for antimony trioxide. One study was available that described the effects of inhalation exposure to antimony trisulfide on rabbits, rats, and dogs (Brieger et al., 1954). A summary of this study is provided below.

Brieger et al. (1954)

Brieger et al. (1954) exposed groups of 6 male rabbits (strain not specified), 10 male Wistar rats and 2 female dogs (strain not specified) to antimony trisulfide for 7 hours/day, 5 days/week for 6-10 weeks. Very limited information was provided regarding the conditions of exposure. The study authors stated that animals were exposed to dust that was similar to an industrial sample obtained from an abrasives facility and that the majority of particles at the height of the nose and mouth of animals were 2 μm in diameter or less. The geometric standard deviation was not reported and no further information was provided. Altered EKG readings, indicative of myocardial damage, were observed in the rabbits exposed to 5.6 mg/m^3 for 6 weeks, rats exposed to 3.07 mg/m^3 for 6 weeks, and dogs exposed to 5.55 mg/m^3 for 10 weeks, but not in dogs exposed to 5.32 mg/m^3 for 7 weeks. Histological evidence of myocardial damage also was observed in the rabbits (flabby myocardium and swelling of myocardial fibers) and rats (focal degenerative changes in myocardium). In the rats, pathological changes were observed in the lungs during the gross necropsy; the alterations were characterized by the study authors as "slight" and consisted of congestion and focal areas of hemorrhage. It is unclear if a microscopic examination of the lungs was conducted. The authors noted that the lung congestion may have been secondary to the heart effects. The LOAELs for myocardial effects in rabbits, rats and dogs exposed to antimony trisulfide for 6, 6 and 10 weeks, respectively, are 5.6, 3.07 and 5.55 mg/m^3 (4.0, 2.2, 4.0 mg/m^3 antimony).

Other Studies

Injection Studies. Intraperitoneal injection studies using antimony potassium tartrate (purity >99.4%) were conducted in F344 rats and B6C3F$_1$ mice (10/sex/group) (NTP, 1992). A 16 day range finding study used doses of 0, 1.5, 3, 6, 11 or 22 mg/kg-day in rats and 0, 6, 13, 25, 50 or 100 mg/kg-day in mice, administered as 12 injections given on consecutive week days. These correspond to doses of 0, 0.6, 1.2, 2.4, 4.4 or 8.8 mg Sb/kg-day in rats and 0, 2.4, 5.2, 10, 20 or 40 mg Sb/kg-day. Mortality was observed in the high dose groups for both rats (3/20) and mice (20/20). Liver lesions, characterized as necrosis and inflammation of the liver capsule, were observed in 7 of 10 mice given 20 mg Sb/kg-day (both sexes). These lesions were not observed in mice from the highest dose group that died prior to the end of the study. Liver necrosis and kidney degeneration were observed in the high dose male rats that died prior to the end of the study. A 13-week injection study used doses of 0, 1.5, 3, 6, 12 or 24 mg/kg-day given 3 times per week, resulting in daily antimony doses of 0, 0.6, 1.2, 2.4, 4.8 or 9.6 mg Sb/kg-day. Mortality was observed in 4 of 10 male rats in the highest dose groups. A reduction in body weight was seen in both male (18%) and female (11%) rats from these groups. Relative liver weight was increased in male and female rats from all dose groups (maximum increase of 20% for males and 40% for females at 9.6 mg Sb/kg-day). Dose-related increases in serum alanine aminotransferase and sorbitol dehydrogenase were also observed in male and female rats (data

presented graphically). Liver degeneration and necrosis were observed in male rats (0/10, 0/10, 0/10, 2/10, 8/10 and 6/8 for 0, 0.6, 1.2, 2.4, 4.8 and 9.6 mg Sb/kg-day, respectively) and in female rats (0/10, 0/10, 0/10, 0/10, 1/10 and 10/10 for 0, 0.6, 1.2, 2.4, 4.8 and 9.6 mg Sb/kg-day, respectively). Kidney degeneration was also observed in the highest dose group in female rats (3/10). No clinical signs of toxicity or gross or microscopic changes were observed in mice exposed to antimony potassium tartrate in this study.

Miranda et al. (2006) evaluated the developmental toxicity and transplacental transfer of meglumine antimoniate (pentavalent compound) following subcutaneous injection in pregnant female Wistar rats (19-21/group). Antimony doses of 0, 75, 150 or 300 mg Sb/kg-day were administered on GD 1-20. Rats were sacrificed by CO_2 inhalation on GD21 and the number of implantation sites, live/dead fetuses, resorptions and corpora lutea were counted. Living fetuses were weighed, measured, examined for gross abnormalities and processed for evaluation of skeletal (staining with Alizarin Red) and visceral abnormalities (micro-sectioning after fixation in Bouin's solution). Maternal blood samples were collected each day from a separate group of rats given 300 mg Sb/kg-day. Fetal blood samples were obtained from the offspring of this group on GD21. Maternal and fetal body weights were reduced in the high-dose group (18% and 10%, respectively, at 300 mg/kg-day). Embryolethality was also observed in this dose group (decreased number of live fetuses). The frequency of dilated ureter was increased in fetuses from the 150 and 300 mg Sb/kg-day dose groups. Skeletal variations were also seen in the mid- and high-dose groups (misaligned sternebrae, supernumerary ribs, misshapened basiooccipital bone). Transplacental transfer of antimony was confirmed by fetal blood analysis with fetal blood concentrations measured to be roughly one-third of the concentrations found in maternal blood.

Alvarez et al. (2005) evaluated the ability of trivalent and pentavalent antimony compounds to induce cardiomyopathy in guinea pigs. Guinea pigs received daily intramuscular injections of pentavalent antimony (16 mg/kg antimony meglumine for 26 days) or trivalent antimony (10 mg/kg antimony potassium tartrate for 8 to 12 days). Controls were given saline injections. Treatment with trivalent antimony caused lethality in approximately 50% of the animals. Survivors exhibited alterations in the EKG (i.e., T-wave flattening and or inversion, depression of the ST segment and elongation of the RR and QT intervals). Ventricular myocytes isolated from these animals showed impaired contraction responses to stimulus, altered whole cell action potential and reduced calcium current. L-Carnitine was investigated as a protective treatment for trivalent antimony cardiotoxicity. Combined treatment of L-carnitine and antimony potassium tartrate produced a delay in antimony-induced mortality. Prior treatment with L-carnitine (for 4 days) followed by combined treatment (for 6 or 12 days) decreased mortality to less than 10% of treated animals. These animals exhibited a normal EKG and isolated myocytes had normal contractility and whole cell action potential. Daily injections of pentavalent antimony for 26 days caused an elongation of the QT interval of the EKG. Mortality was not induced by pentavalent antimony treatment in this study and ventricular myocytes were not isolated from these animals.

Genotoxicity Studies. The genotoxic potential of soluble antimony compounds is difficult to assess, given the conflicting results of published studies. Antimony compounds were generally negative in bacterial and mammalian cell mutagenicity assays. Both positive and negative

findings were reported for in vitro DNA damage, chromosome aberrations and micronucleus formation in mammalian cells. Conflicting data were also available for *in vivo* studies of micronucleus formation. Genotoxicity data are presented in Table 1.

Antimony trichloride, antimony pentachloride and antimony potassium tartrate were negative for reverse mutation in *Salmonella typhimurium* (Kanematsu et al., 1980; Kuroda et al., 1991; Zeiger et al., 1992). Antimony trichloride was also negative for reverse mutation in *Escherichia coli* (Kanematsu et al., 1980). Antimony trichloride and antimony pentachloride were negative in an early rec assay for differential killing in DNA repair-proficient and DNA repair-deficient strains of *Bacillus subtilis* conducted using the streak method (Nishioka, 1975), but gave strong positive results in more recent rec assays conducted using more sensitive methods (Kanematsu et al., 1980; Kuroda et al., 1991). Stibine (SbH_3) and trimethyl stibine (Me_3Sb) produced DNA damage in a plasmid DNA nicking assay (pBr 322 plasmid DNA) (Andrewes et al., 2004). Potassium antimony tartrate, hexahydroxyantimonate and trimethylantimony dichloride produced negative results in this assay system.

Studies in mammalian cells have sometimes reported positive results for antimony compounds. Antimony trichloride increased the frequency of micronuclei and caused DNA strand breaks in isolated human lymphocytes (Schaumloffel and Gebel, 1998). Antimony sodium tartrate produced an increase in the number of chromatid breaks in cultured human leukocytes (Paton and Allison, 1972). Antimony acetate increased viral transformation in Syrian hamster embryo cells *in vitro* (Casto et al., 1979). Antimony trichloride increased SCE in V79 Chinese hamster cells *in vitro*, although antimony pentachloride did not (Kuroda et al., 1991). Antimony trichloride increased micronucleus formation and induced DNA strand breaks in V79 Chinese hamster cells, but did not cause DNA-protein crosslinks in these cells (Gebel et al., 1998). Huang et al. (1998) also demonstrated that antimony trichloride increased micronucleus formation in Chinese hamster ovary cells, human bronchial epithelial cells and human fibroblasts. Delayed apoptosis was also observed in these cell types following treatment with antimony trichloride. Antimony trisulfide produced chromosomal aberrations in Chinese hamster ovary (CHO) cells *in vitro*, but did not produce gene mutation in the CHO cells or neoplastic transformation in BALB/c-3T3 cells (Tu and Sivak, 1984). Antimony trichloride and antimony potassium tartrate inhibited the repair of radiation-induced double-strand breaks in CHO cells (Takahashi et al., 2002). Gurnani et al. (1992) reported that antimony trichloride produced chromosomal aberrations in mouse bone marrow *in vivo*.

Potassium antimony tartrate was shown to decrease the growth of several lymphoid cell lines through caspase- and reactive oxygen species-dependent apoptosis (Lecureur et al., 2002a, 2002b). Wyllie and Fairlamb (2006) showed that trivalent antimony (as potassium antimony tartrate) was toxic to THP-1 macrophages from a human leukemia monocyte cell line. Trivalent antimony significantly altered thiol homeostasis in these cells, suggesting that this may be a key event in the mode of action of antimonials against leukemia cells. The pentavalent antimony compound sodium stibogluconate did not affect thiol status and was not toxic to macrophages in this study.

Table 1. Genotoxicity Data for Antimony Compounds

Test System/ Endpoint	Results		Reference
	Positive	Negative	
Salmonella typhimurium/ reverse mutation	None reported	antimony trichloride, antimony pentachloride, antimony potassium tartrate	Kanematsu et al. (1980); Kuroda et al. (1991); Zeiger et al. (1992)
Escherichia coli/ reverse mutation	None reported	antimony trichloride	Kanematsu et al. (1980)
Bacillus subtilis/ Rec assay	antimony trichloride, antimony pentachloride	antimony trichloride, antimony pentachloride	Kanematsu et al. (1980); Kuroda et al. (1991); Nishioka (1975)
Plasmid DNA nicking assay	stibine and trimethyl stibine	potassium antimony tartrate, hexahydroxyantimonate and trimethylantimony dichloride	Andrewes et al. (2004)
Human peripheral lymphocytes/ micronucleus formation	antimony trichloride	None reported	Schaumloffel and Gebel (1998)
Human peripheral lymphocytes/DNA strand breaks	antimony trichloride	None reported	Schaumloffel and Gebel (1998)
Human leukocytes/chromatid breaks	antimony sodium tartrate	None reported	Paton and Allison (1972)
Syrian hamster embryos/viral transformation	antimony acetate	None reported	Casto et al., (1979)
V79 Chinese hamster cells/SCE	antimony trichloride	antimony pentachloride	Kuroda et al. (1991)
V79 Chinese hamster cells/micronucleus formation, DNA strand breaks	antimony trichloride	None reported	Gebel et al. (1998)
V79 Chinese hamster cells/DNA-protein crosslinks	None reported	antimony trichloride	Gebel et al. (1998)
Chinese hamster ovary (CHO) cells, human bronchial epithelial cells, human fibroblast/ micronucleus formation	antimony trichloride	None reported	Huang et al. (1998)
CHO cells/ chromosome aberrations	antimony trisulfide	None reported	Tu and Sivak (1984)
CHO cells/gene mutation	None reported	antimony trisulfide	Tu and Sivak (1984)
BALB/c-3T3 cells/neoplastic transformation	None reported	antimony trisulfide	Tu and Sivak (1984)
CHO cells/inhibition of DNA repair	antimony trichloride, antimony potassium tartrate	None reported	Takahashi et al. (2002)
Mouse bone marrow in vivo/chromosome aberrations	antimony trichloride	None reported	Gurnani et al. (1992)

DERIVATION OF A PROVISIONAL SUBCHRONIC AND CHRONIC RfD FOR SOLUBLE ANTIMONY COMPOUNDS

Subchronic RfD

Repeated-dose oral exposure studies in animals have been conducted using potassium antimony tartrate (Omura et al., 2002; Poon et al., 1998; NTP, 1992; Schroeder et al., 1970; Schroeder et al., 1968; Kanisawa and Schroeder, 1969) and antimony trichloride (Marmo et al., 1987; Rossi et al., 1987; Angrisani et al., 1988). Table 2 presents a summary of the noncancer results for the oral studies using soluble antimony compounds in experimental animals.

The subchronic toxicity study by Poon et al. (1998) found only mild adaptive changes in rats, even at the high dose of 18 mg Sb/kg-day. Similarly, the short-term study by NTP (1992) found only minor changes at doses as high as 67 mg Sb/kg-day in rats. NTP (1992) reported more toxic effects in mice treated with high doses for 4 weeks, but effect levels could not be identified due to inadequate reporting of results. Much lower doses were reported to produce decreases in maternal and pup body weight with gestational and postnatal exposure in rats (Rossi et al., 1987) and reductions in body weight and survival in rats and mice exposed to antimony in the drinking water for life (Schroeder et al., 1968; Kanisawa and Schroeder, 1969; Schroeder et al., 1970). The lowest LOAELs were observed in the chronic studies.

The chronic drinking water studies with potassium antimony tartrate in rats and mice evaluated survival, body weight changes, limited clinical chemistry parameters (serum glucose and cholesterol), and findings of gross lesions at necropsy (Schroeder et al., 1968, 1970; Kanisawa and Schroeder, 1969). The discrepancy in effect levels between the chronic and shorter-duration studies is a source of uncertainty, as is the uncorroborated report of effects on maternal and pup body weights in rats exposed to low doses during and after gestation. Therefore, the chronic drinking water studies, which reported the lowest LOAELs in the database, were selected as critical studies for evaluating the potential effects of subchronic exposure to soluble antimony compounds. Decreased body weight gain, reduced survival, and altered serum chemistry (decreased serum glucose) were seen in rats chronically exposed to potassium antimony tartrate in the drinking water. In the Poon et al. (1998) study, hepatotoxicity and thyroid toxicity reported in the high dose-exposure group were also reported in control rats, and other toxicological changes observed in the high dosage group are quite comparable to the similar effects seen in chronic rodent studies. The critical effects observed at lower doses in chronic and developmental studies are therefore considered appropriate for subchronic duration. The chronic oral RfD of 4E-4 mg/kg-day for antimony on IRIS (U.S. EPA, 2007) is based on a LOAEL of 0.35 mg Sb/kg-day for reduced life span and serum chemistry changes in male and female rats exposed to potassium antimony tartrate in drinking water for 2 years by Schroeder et al. (1970). This value was adopted as the **subchronic p-RfD (4E-4 mg Sb/kg-day)** for soluble antimony compounds.

The subchronic provisional RfD value for soluble antimony (based on the metal content) is appropriate for antimony potassium tartrate (CASRN 11071-15-1) and antimony trichloride (CASRN 10025-91-9) but not oxides of antimony and may not be applicable for other salts.

Table 2. Repeated-Dose Oral Toxicity Studies for Soluble Antimony Compounds

Species	Dose/duration	NOAEL (mg Sb/kg-day)	LOAEL (mg Sb/kg-day)	Effect	Reference
Crj:Wistar rats (7-8 males/ group)	oral gavage (3 days/week for 4 weeks) with antimony potassium tartrate; 0 or 10 mg Sb/kg-day	10	NA	No effects on reproductive tissues or body weight	Omura et al., 2002
Cjr:CD-1 mice (8-10 males/ group)	oral gavage (5 days/week for 4 weeks) with antimony potassium tartrate; 0 or 10 mg Sb/kg-day	10	NA	No effects on reproductive tissues or body weight	Omura et al., 2002
F344 rats (5/sex/group)	14-day drinking water study with antimony potassium tartrate; 0, 6, 11, 24, 38 or 67 mg Sb/kg-day	67	NA	Increased relative liver and kidney weights with no histological changes	NTP, 1992
B6C3F1 mice (5/sex/group)	14-day drinking water study with antimony potassium tartrate; 0, 24, 39, 70, 109 or 163 mg Sb/kg-day	NA	NA	Decreased body weight, clinical signs, histological changes (liver, forestomach) at high dose; unclear if clinical signs also at lower doses	NTP, 1992
Male and female Sprague Dawley rats (15/sex/group)	13-week drinking water study with antimony potassium tartrate; 0, 0.024, 0.22, 2.2 or 17 mg Sb/kg-day for male rats; 0, 0.024, 0.25, 2.4 or 18 mg/kg-day for female rats	18	NA	Mild adaptive histological changes (liver, thyroid, thymus, spleen, pituitary)	Poon et al., 1998
Male and female Long Evans rats (51-59/sex/group)	Lifetime drinking water exposure to antimony potassium tartrate; 0 or 0.29 mg Sb/kg-day for males and 0 or 0.35 mg Sb/kg-day for females	NA	0.35	Reduced survival	Schroeder et al., 1970
CD mice (54-55/sex/group)	Lifetime drinking water exposure to antimony potassium tartrate; 0.35 mg Sb/kg-day	NA	0.35	Body weight reduction	Schroeder et al., 1968; Kanisawa and Schroeder, 1969
Pregnant female NOS albino rats (30/group); rat pups (36-90/group)	Maternal drinking water exposure to antimony trichloride during gestation; 0, 0.075 and 0.75 mg Sb/kg-day	0.075	0.75	Decreased maternal and offspring body weight	Rossi et al., 1987

Chronic RfD

The **chronic RfD of 4E-4 mg/kg-day** for antimony is available on IRIS (U.S. EPA, 2007).

FEASIBILITY OF DERIVING A PROVISIONAL SUBCHRONIC AND CHRONIC RfC FOR SOLUBLE ANTIMONY COMPOUNDS

Most of the available data on the toxicity of inhaled antimony is from occupational and animal studies involving exposure to antimony trioxide. These studies are described in a separate provisional toxicity value report for antimony trioxide. Brieger et al. (1954) found evidence of myocardial damage (altered EKG readings) in workers occupationally exposed to 0.58-5.5 mg/m^3 antimony trisulfide and in rabbits, rats and dogs exposed to 3-6 mg/m^3 antimony trisulfide for 6-10 weeks. Very limited information was provided in this study regarding the conditions of exposure, and available dose response information was insufficient for the derivation of an inhalation RfC for either subchronic or chronic durations.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR SOLUBLE ANTIMONY COMPOUNDS

Weight-of-Evidence Descriptor

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "inadequate information to assess carcinogenic potential" of soluble antimony salts. Available studies have found no evidence of carcinogenic activity by soluble antimony compounds. However, the available studies were of inadequate experimental design to draw any conclusions from the results. In the lifetime oral studies of antimony in rats and mice reported by Schroeder's group (Schroeder et al., 1968; Kanisawa and Schroeder, 1969; Schroeder et al., 1970), there was no evidence of compound-related tumor formation when Long Evans rats and CD mice were exposed in drinking water to a single concentration of potassium antimony tartrate (providing 5 ppm antimony). Although some effects on survival were seen in the rats exposed to antimony and some treatment-related reductions in body-weight gain were noted in the mice, exposure to antimony appeared to have no effect on the formation of gross tumors detectable at necropsy. These studies were limited by the use of a single dose level and use of gross necropsy alone to monitor tumor formation. Some studies suggest that certain antimony compounds may be clastogenic; however, compounds were generally negative in bacterial mutagenicity assays (see *Genotoxicity Studies* above). Also, some studies suggest that antimony potassium tartrate may induce apoptosis through caspase- and reactive oxygen species-dependent processes (Lecureur et al., 2002a, 2002b; Huang et al., 1998). Soluble trivalent antimony compounds have been shown to cause apoptosis in leukemia cells and are being investigated as a novel therapy in the treatment of this disease (Wyllie and Fairlamb, 2006; Lecureur et al., 2002a, 2002b).

A separate provisional toxicity value report is available for antimony trioxide, which was found to have "suggestive evidence of the carcinogenic potential" by the inhalation route of exposure, based on human and animal studies.

Quantitative Estimates of Carcinogenic Risk

There are no appropriate human or animal data from which to derive an oral slope factor or inhalation unit risk for soluble antimony compounds.

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