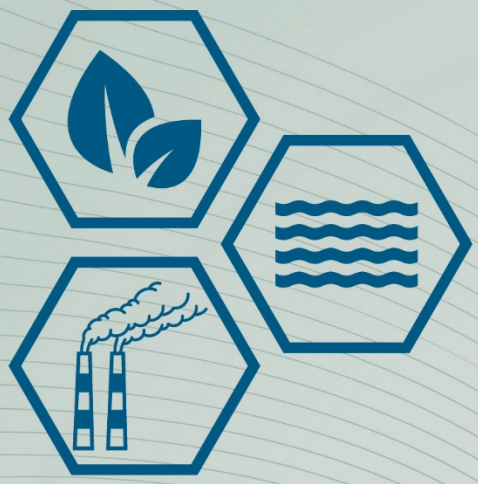

Toxicological Profile for Antimony and Compounds

October 2019

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

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September 1992	Final toxicological profile released

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The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Antimony (Sb) is naturally present in the earth's crust at levels of about 0.2–0.3 mg/kg (ppm), but these levels vary by location (Telford et al. 2008). It can be transported into streams and waterways from natural weathering of soil, as well as from anthropogenic sources (EPA 1979; Mok and Wai 1990). Antimony enters the environment during the mining and processing of antimony-containing ores and in the production of antimony metal, alloys, antimony oxide, and combinations of antimony with other substances (Grund et al. 2012; Li et al. 2011). Antimony was mined in the United States; however, the last mine closed in 2001 (HSDB 2005a). Impure antimony ore and metal are imported into the United States from other countries for processing (USGS 2015). Small amounts of antimony are released into the environment by incinerators and coal-burning power plants (Belzile et al. 2011). Studies indicate that antimony is retained in the soil through adsorption and can sorb onto clay minerals, oxides, and hydroxides in the soil and aquatic sediment (Wilson et al. 2010).

Antimony is predominantly in the +5 oxidation state in both aerobic freshwater and seawater. These waters also contain antimony in the +3 oxidation state to a lesser extent. Trivalent antimony is the dominant oxidation state of antimony in anaerobic environments. The predominant trivalent species in the environment is antimony trihydroxide ($Sb(OH)_3$) and the predominant pentavalent species is hexahydroxoantimonate ($Sb(OH)_6^-$), as predicted by thermodynamic calculations (Bodek et al. 1988).

Antimony can be reduced and methylated by microorganisms in anaerobic sediment, releasing volatile methylated antimony compounds into the water. Multiple microorganisms have been found to methylate antimony in the soil and water and other anaerobic environments (Bentley and Chasteen 2002).

The general population is exposed to low levels of antimony from ingestion of food and drinking water and possibly by inhalation of particulate matter containing antimony in ambient air (Belzile et al. 2011). Occupational exposures of antimony may occur at smelters, coal-fired plants, and refuse incinerators that process or release antimony. A comparison of urinary antimony concentrations in the U.S. population between 1999 and 2016 suggests that there was a marked decrease in exposure levels between 1999 and 2006, as the urinary antimony levels decreased 40–50% in this time period (CDC 2019). After 2006, there were little changes in urinary antimony levels (CDC 2019), suggesting stable environmental levels.

1.2 SUMMARY OF HEALTH EFFECTS

Antimony and its compounds are among the oldest known remedies in the practice of medicine and they have been used to treat a variety of illnesses over the last 600 years. Currently, antimony compounds are used to treat the parasitic disease leishmaniasis. Toxic side effects in humans following intraperitoneal, intravenous, or intramuscular injection of an antimony-containing drug have been reported, including altered electrocardiograms (EKGs), vomiting, diarrhea, and joint and/or muscle pain (Andersen et al. 2005; Dancaster et al. 1966; Lawn et al. 2006; Neves et al. 2009; Palacios et al. 2001; Sundar et al. 1998; Thakur 1998; Zaki et al. 1964). These side effects are more frequently observed following administration of trivalent antimony compounds, especially antimony potassium tartrate or antimony sodium tartrate; side effects have also been found in humans administered pentavalent organic compounds such as sodium antimony gluconate or meglumine antimoniate (Dancaster et al. 1966; Honey 1960; Neves et al. 2009).

Adverse health effects have also been observed in humans and animals following inhalation, oral, or dermal exposure to antimony and antimony compounds. These studies predominantly assessed the toxicity of trivalent antimony compounds, particularly antimony trioxide and antimony potassium tartrate. As illustrated in Figures 1-1 and 1-2, the most sensitive targets appear to be the respiratory tract, heart, gastrointestinal tract, serum glucose, and developing animal. A systematic review of these endpoints resulted in the following hazard identification conclusions:

- Respiratory effects following inhalation exposure are a presumed health effect for humans
- Myocardial effects and EKG alterations are a suspected health effect for humans
- Gastrointestinal effects are a presumed health effect for humans
- Developmental effects are a suspected health effect for humans
- Alterations in blood glucose levels are a suspected health effect for humans

Other health effects that have been observed in animals orally exposed to higher doses of antimony include hepatocellular vacuolization (NTP 1992), hematological alterations including decreases in red blood cell counts (Poon et al. 1998) and hemoglobin levels (Sunagawa 1981), and histological alterations in the thyroid (Poon et al. 1998).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Antimony

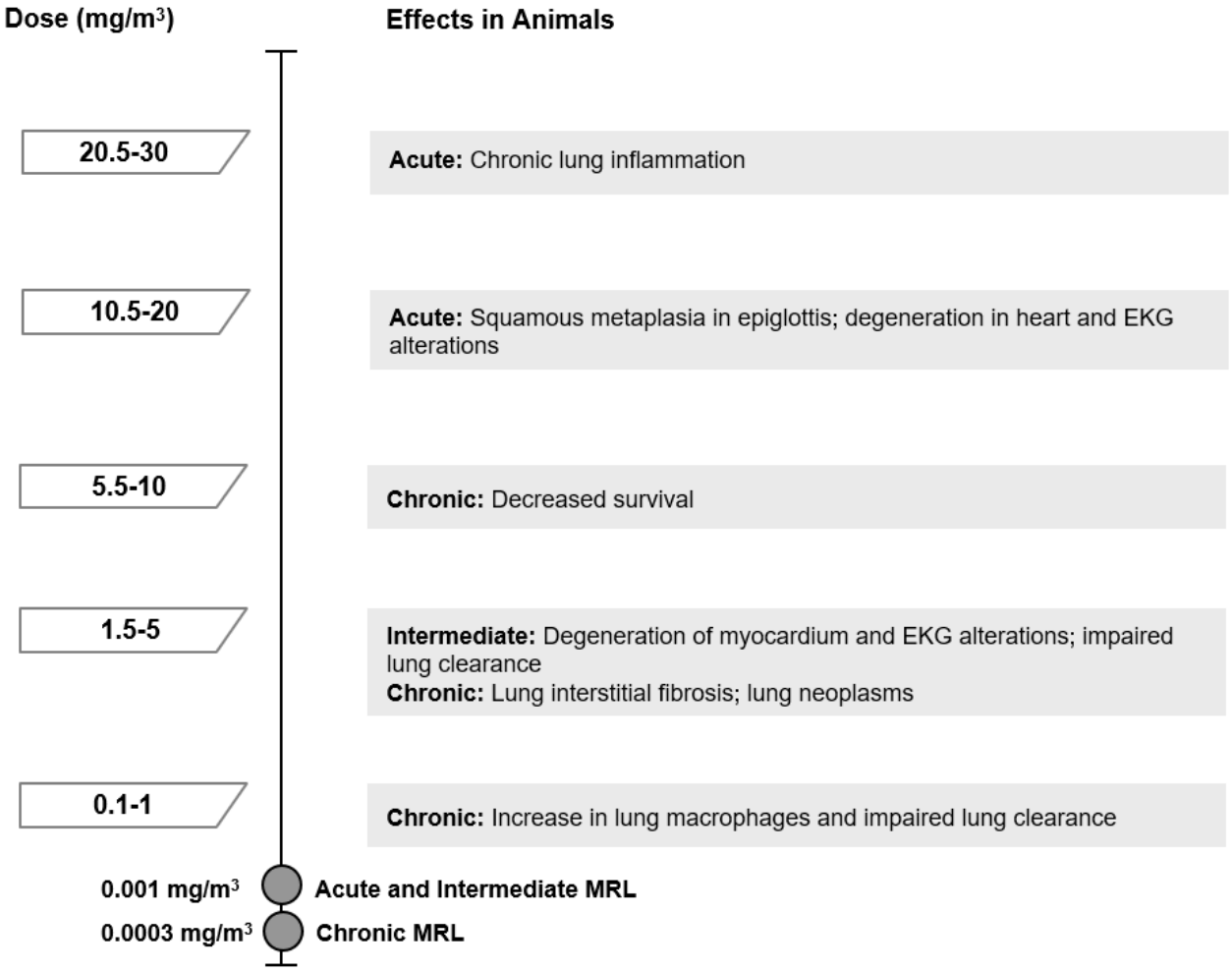
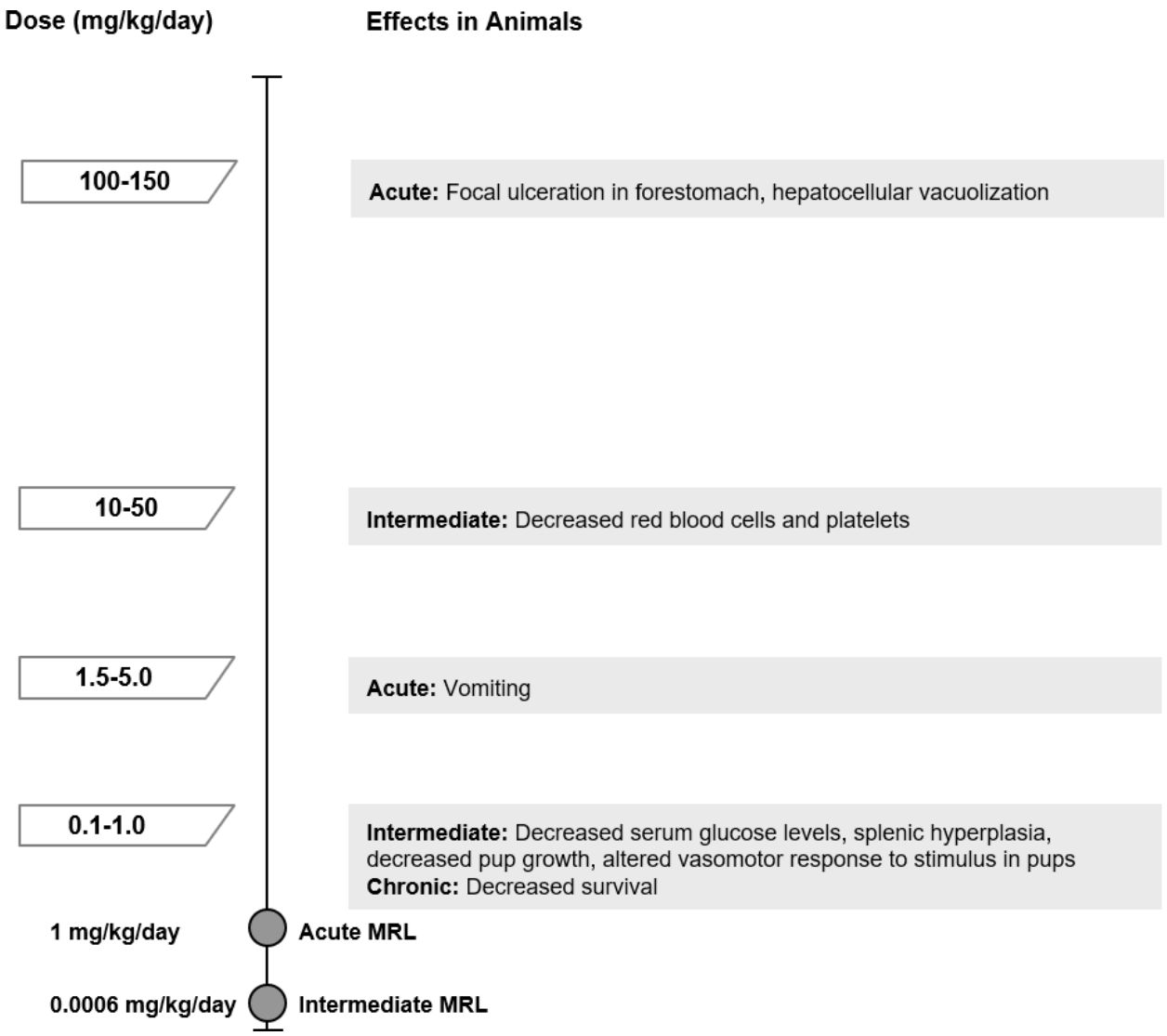


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Antimony



Dermatosis and ocular irritation have been reported in workers exposed to airborne antimony (Potkonjak and Vishnijich 1983; Stevenson 1965). The dermatitis was seen more often during the summer months and in workers exposed to high temperatures. It is probably the result of antimony being dissolved in sweat and penetrating the sweat glands (Stevenson 1965). In general, dermal effects have not been observed in animal studies. Animal studies do provide support for antimony being considered an ocular irritant. Eye irritation has been reported in animals exposed to stibine gas (NIOSH 1979) and following instillation of antimony thioantimonate into rabbit eyes (Horton et al. 1986). Additionally, increases in corneal opacities and cataracts have been observed in animals repeatedly exposed to airborne antimony trioxide (Newton et al. 1994).

Respiratory Effects. The lung is the primary target of toxicity within the respiratory tract, and effects are observed following acute-, intermediate-, and chronic-duration inhalation exposure. In antimony workers, pneumoconiosis (Cooper et al. 1968; Potkonjak and Pavlovich 1983) and clinical signs such as coughing and laryngitis (Potkonjak and Pavlovich 1983; Renes 1953) have been reported. A relationship between exposure level and effect cannot be established from these data because the workers were also exposed to other compounds, including arsenic oxide, iron oxide, hydrogen chloride, and hydrogen sulfide. In laboratory animals, the lung effects include the accumulation of antimony particles in the lungs, increases in alveolar/intra-alveolar macrophages (Newton et al. 1994; NTP 2016), decreases in antimony lung clearance times (Newton et al. 1994), chronic interstitial inflammation (Brieger et al. 1954; Newton et al. 1994; NTP 2016), and interstitial fibrosis (Groth et al. 1986; Newton et al. 1994; Watt 1983). Lung effects have been found in rats, mice, and rabbits following inhalation exposure to antimony trioxide, antimony trisulfide, and antimony ore; lung effects have also been observed in laboratory animals following exposure to stibine gas. Intermediate- and chronic-duration studies (Newton et al. 1994) demonstrated that pulmonary damage can occur postexposure due to the persistence of the antimony trioxide in the lung. At the end of a 13-week or 1-year exposure to antimony trioxide, histological alterations in the lungs were limited to increases in alveolar/intra-alveolar macrophages; however, after 27-week or 1-year recovery periods, respectively, interstitial inflammation and fibrosis were observed. Other respiratory effects that have been observed in some studies include squamous metaplasia of the epiglottis (NTP 2016) and hyperplasia of the nasal respiratory epithelium (NTP 2016). The lowest lowest-observed-adverse-effect levels (LOAELs) for respiratory tract effects following acute-, intermediate-, and chronic-duration exposures are 12 mg Sb/m^3 as antimony trioxide (NTP 2016), 4.11 mg Sb/m^3 as antimony trioxide (Newton et al. 1994), and 1.6 mg Sb/m^3 as antimony trioxide (Watt 1983), respectively.

Cardiovascular Effects. In workers exposed to antimony trisulfide dust, EKG alterations were found in about 50% of the workers (Brieger et al. 1954). A small number of animal studies included EKG readings; these studies reported alterations in rats, rabbits, and dogs exposed to airborne antimony trisulfide (Brieger et al. 1954). Two studies of National Health and Nutrition Examination Survey (NHANES) participants have not found associations between urinary antimony levels and heart disease or peripheral arterial disease (Guo et al. 2016; Navas-Acien et al. 2005). No alterations were observed in guinea pigs or pigs exposed to airborne antimony trioxide for intermediate or chronic durations (Dernehl et al. 1945; Watt 1983). These findings are supported by reports of altered EKG readings (particularly prolongation of the QT interval) in individuals exposed to repeated injections of antimony (Dancaster et al. 1966; Honey 1960; Pandey et al. 1988) and in experimental studies in laboratory animals injected with trivalent or pentavalent antimony compounds (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966).

Gastrointestinal Effects. Historically, antimony has been known for its emetic properties. Abdominal pain, vomiting, nausea, and ulcers have been observed in antimony workers (Brieger et al. 1954; Renes 1953; Taylor 1966). Gastrointestinal effects have also been observed in humans receiving intramuscular injections of antimony (Harris 1956; Zaki et al. 1964). Vomiting has also been observed in dogs following acute oral exposure (Houpt et al. 1984), and chronic inflammation and/or ulceration was observed in the forestomach of mice following acute oral exposure to antimony potassium tartrate (NTP 1992) or chronic inhalation exposure to antimony trioxide (NTP 2016). Overt signs of gastrointestinal irritation or histological alterations of the gastrointestinal tract have not been observed in numerous inhalation or oral exposure studies in rats.

Developmental Effects. The developmental toxicity of antimony has not been extensively evaluated in humans or animals. Decreases in growth have been reported in the infants of female antimony workers (Belyaeva 1967); interpretation of the results of this study is limited by the lack of study details, particularly regarding the control group, antimony concentrations in the facility, type of work the women performed, and potential exposure to other compounds. A general population study did not find associations between maternal or paternal urinary antimony levels and birth outcomes (Bloom et al. 2015). Studies in animals support the findings of the occupational exposure study. Decreases in pup growth were observed in the offspring of rats orally exposed to antimony trichloride during gestation and lactation (Rossi et al. 1987), and decreases in birth weight or fetal weight were observed in rats administered organic pentavalent antimony compounds via subcutaneous or intramuscular injection (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006) or administered antimony trichloride

via intramuscular injection (Alkhawajah et al. 1996). Antimony does not appear to result in external or skeletal abnormalities in rats following oral or parenteral administration. Exposure to antimony during gestation and/or lactation and post-weaning exposure has resulted in impaired vasomotor response to 1-noradrenaline, 1-isoprenaline, and acetylcholine in 30- and 60-day-old rat pups (Angrisani et al. 1988; Rossi et al. 1987).

Blood Glucose Levels. A study of NHANES participants found associations between urinary antimony levels and the risk of diabetes (Menke et al. 2016). There are some data to indicate that antimony decreases blood glucose levels following intermediate or chronic oral exposure in rats (Poon et al. 1998; Schroeder et al. 1970), with supporting data from an intermediate-duration study finding decreased blood glucose levels in rats administered intramuscular injections of organic pentavalent compounds (Alkhawajah et al. 1992).

Cancer Effects. Two occupational exposure studies examining carcinogenicity of antimony have found increases in lung cancer deaths (Jones 1994; Schnorr et al. 1995). An association between drinking water antimony levels and cancer incidences was also reported (Colak et al. 2015). Two studies of NHANES participants did not find associations between urinary antimony levels and cancers (Guo et al. 2016; Mendy et al. 2012). Mixed results have been found in chronic inhalation studies in rats. Increases in lung neoplasms were observed in rats exposed to 4.2 or 36 mg Sb/m^3 as antimony trioxide for approximately 1 year (Groth et al. 1986; Watt 1983). A third 1-year exposure study (followed by a 1-year recovery) did not find lung neoplasms in rats exposed to 3.8 mg Sb/m^3 (Newton et al. 1994). A 2-year inhalation study conducted by the National Toxicology Program (NTP 2016) found increases in the incidence of alveolar/bronchiolar adenomas in rats at 8.3 mg Sb/m^3 and alveolar/bronchiolar adenomas and carcinomas in mice at 2.5 mg Sb/m^3. No increases in tumors were found in rats or mice following lifetime oral exposure to antimony potassium tartrate (Kanisawa and Schroeder 1969; Schroeder et al. 1970). The Department of Health and Human Services (HHS) has categorized antimony trioxide as reasonably anticipated to be a human carcinogen (NTP 2018). The International Agency for Research on Cancer (IARC 2015) categorized antimony trioxide in group 2B (possibly carcinogenic to humans) and antimony trisulfide in group 3 (not classifiable as to its carcinogenicity to humans). The EPA have not classified the carcinogenicity of antimony.

1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, the available inhalation data for antimony suggest that the respiratory tract is the most sensitive target of toxicity in laboratory animals. The available oral data for antimony suggest that the gastrointestinal tract, liver, and serum glucose levels are the most sensitive targets of toxicity in laboratory animals (see Figure 1-4). As summarized Table 1-1, inhalation MRLs have been derived for acute-, intermediate-, and chronic-duration exposure to antimony and oral MRLs have been derived for acute- and intermediate-duration exposure to antimony. The database was considered inadequate for derivation of a chronic-duration oral MRL. Refer to Appendix A for detailed information regarding MRL derivation.

Figure 1-3. Summary of Sensitive Targets of Antimony – Inhalation

The respiratory tract is the most sensitive target of antimony inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.

Figure 1-4. Summary of Sensitive Targets of Antimony – Oral

The gastrointestinal tract, liver, and serum glucose levels are the most sensitive targets of antimony oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose-response data were available for humans.

Table 1-1. Minimal Risk Levels (MRLs) for Antimony[a]

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

[a]See Appendix A for additional information.
[b]Uncertainty factors: 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability.
[c]Uncertainty factors: 10 for extrapolation from animals to humans and 10 for human variability.

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

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of antimony. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to antimony, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to antimony was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Tables 2-1 and 2-2. Animal inhalation studies are presented in Table 2-3 and Figure 2-2, animal oral studies are presented in Table 2-4 and Figure 2-3, and animal dermal studies are presented in Table 2-5.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress

or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of antimony are indicated in Table 2-3 and Figure 2-2.

A User's Guide has been provided at the end of this profile (see Appendix D). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

The health effects of antimony (Sb) have been evaluated in epidemiological and laboratory animal studies following inhalation, oral, or dermal exposure. As summarized in Figure 2-1, 48% of these studies involved oral exposure, 37% involved inhalation exposure, and the remaining 15% were dermal and ocular exposure studies. Most of the studies involved intermediate- or chronic-duration exposure, and body weight, respiratory tract, and cardiovascular systems were the most studied endpoints. In addition to these studies, there are numerous studies in humans and animals involving parenteral administration of antimony compounds.

Trivalent and pentavalent antimony compounds have been used for the treatment of parasitic diseases, particularly leishmaniasis and schistosomiasis, for over 100 years. Although trivalent antimony in the form of potassium or sodium antimony tartrate was first used, it was later discontinued due to the side effects. Pentavalent organic antimony compounds have been used for the last 60 years. The two predominant forms are sodium antimony gluconate (sodium stibogluconate) and meglumine antimoniate (*N*-methyl-D-glucamine or Glucantime) (Haldar et al. 2011). In the treatment of parasitic diseases, the patient receives multiple injections of the antimony compounds. Numerous investigators have reported adverse effects associated with these treatments. These studies provide useful information for identifying potential targets of antimony toxicity, although the relevance to environmental exposure is not known

given the poor absorption of antimony compounds following inhalation, oral, or dermal exposure (see Section 3.1.1). The primary targets of toxicity appear to the heart (alterations in EKG readings), gastrointestinal tract (nausea, abdominal pain, vomiting, diarrhea, anorexia), musculoskeletal system (myalgia, arthralgia), liver (increases in alanine and aspartate aminotransferases), pancreas (increases in serum amylase levels), and nervous system (headache, dizziness) (Andersen et al. 2005; Dancaster et al. 1966; Lawn et al. 2006; Neves et al. 2009; Palacios et al. 2001; Sundar et al. 1998; Thakur 1998; Zaki et al. 1964).

Health effects data for all antimony compounds are discussed together in this chapter. There is some evidence of compound-specific differences in toxicity that are likely reflective of toxicokinetic differences, particularly differences in the relative absorption of the compounds. When relevant, these differences are discussed. Concentrations and doses in the tables and text have been calculated from the investigated compound to the elemental antimony in order to facilitate comparisons between studies.

The inhalation, oral, and dermal exposure studies in humans and animals suggest several sensitive targets of antimony toxicity:

- **Respiratory Endpoints:** Antimony is presumed to cause respiratory effects following inhalation exposure based on low evidence in workers exposed to antimony oxides and a high level of evidence in several animal species exposed to antimony trioxide, antimony trisulfide, and antimony ore. The respiratory effects include irritation of epiglottis epithelium, increases in the number of alveolar/bronchiolar macrophages, decreases in lung clearance, and lung interstitial fibrosis.

- **Cardiovascular Endpoints:** Antimony is suspected to cause myocardial damage and EKG alterations based on inadequate evidence in an inhalation occupational exposure study and low evidence in inhalation and oral exposure studies in animals. This hazard identification conclusion is supported by numerous reports of cardiovascular effects in patients administered antimony compounds for the treatment of leishmaniasis and injection studies in animals.

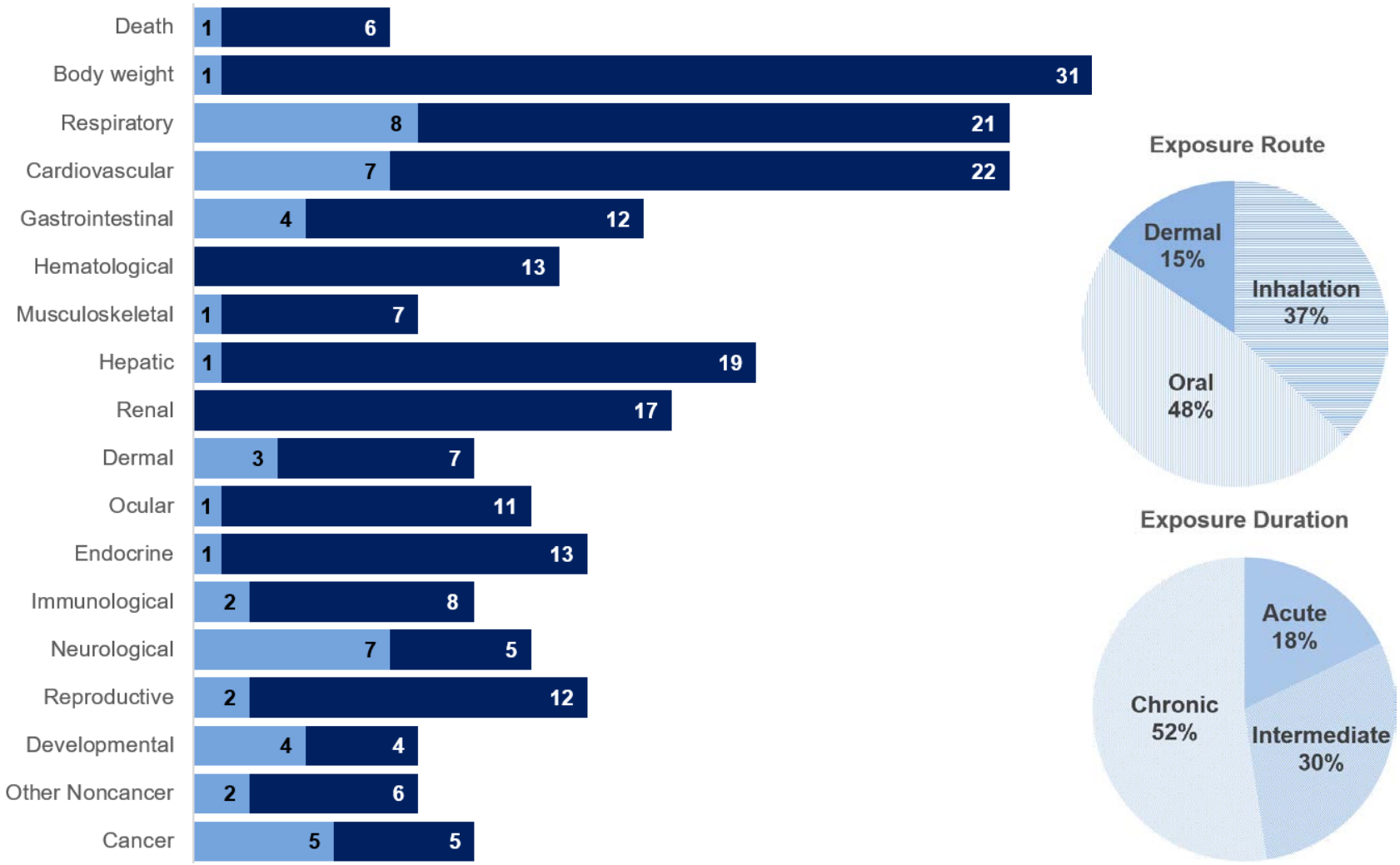
- **Gastrointestinal Endpoints:** Antimony is presumed to cause gastrointestinal tract irritation based on inadequate evidence in human studies and high evidence in animal studies. Observed gastrointestinal effects include nausea and vomiting and forestomach ulceration.

- **Serum Glucose Endpoints:** Antimony is suspected to cause decreases in serum glucose levels based on high evidence from two animal oral exposure studies, supported by an animal intramuscular exposure study; human data are lacking.

- **Developmental Endpoints:** Antimony is suspected to cause developmental effects based on inadequate evidence in humans and high evidence in a small number of animal studies. Developmental effects observed in laboratory animals included decreases in pup growth and alterations in vasomotor reactivity in pups.

Figure 2-1. Overview of the Number of Studies Examining Antimony Health Effects

Most studies examined the potential body weight, respiratory, and cardiovascular effects of antimony
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 53 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Belyaeva 1967	Female workers at an antimony metallurgical facility; some of the women worked in a more dusty section of the facility. A control group was also examined; however, no information was provided whether the controls were matched to the exposed group or whether they had similar jobs without antimony exposure. The number of subjects was not reported; antimony levels were measured in 308 and 115 blood samples from workers and controls, respectively.	**Exposure:** Workers were exposed to metallic antimony, antimony trioxide, and antimony pentasulfide. The antimony levels in the blood and urine were 0.5–20.2 and 0.5–18.2 mg/dL, respectively, in the workers in the dusty section of the facility and 0.5–18.2 mg/L and 0.5–16.2 mg/dL, respectively, in the less dusty section. The blood antimony level in the control group ranged from 0 to 3.3 mg/dL. **Confounding exposure:** Co-exposure to other chemicals was likely but not discussed.	**Reproductive effects:** Reproductive disturbances were reported in 77.5% of the workers and 56% of controls. Increases in the occurrence of disturbances in the menstrual cycle were found (61.2% in workers and 35.7% in controls). Increases in spontaneous abortion (12.5%) were found in the workers, as compared to controls (4.1%). **Developmental effects:** Decreases in infant body weight gain among infants born to workers were observed beginning at 6 months of age. By 12 months of age, infants of workers weighed 8.96 kg compared to 10.05 kg in the controls.
Brieger et al. 1954	112 workers involved in the production of grinding wheels. Workers were employed for 8 months to 2 years. No control group was used.	**Exposure:** Antimony trisulfide levels ranged from 0.42 to 3.9 mg Sb/m^3, with the majority of the findings >2.2 mg Sb/m^3. **Confounding exposure:** Workers were also exposed to phenol formaldehyde resin.	**Respiratory effects:** No signs of respiratory irritation were reported. **Cardiovascular effects:** Altered EKG readings (mostly T waves) were found in 37/75 workers. Increased blood pressure was observed in 14/112 workers and low blood pressure was observed in 24/112 workers; significance of these findings are not known since there was no control group. **Gastrointestinal effects:** A higher incidence of ulcers were found in the antimony exposed workers (63 per 1,000) compared to the total plant population (15 in 1,000).
Cooper et al. 1968	28 antimony process workers involved in extraction of antimony ore to antimony trioxide. Workers employed for 1–15 years. No control group was used.	**Exposure:** Antimony trioxide levels ranged from 0.081 to 138 mg Sb/m^3 at 47 locations within the facility. **Confounding exposure:** Co-exposure to other chemicals was likely but not discussed	**Respiratory effects:** No consistent alterations in lung function (only 14 subjects were examined). Pneumoconiosis was confirmed in three workers and suspected in five other workers.

Table 2-1. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Jones 1994	Retrospective cohort mortality study of 192 workers involved in the production of antimony metal, antimony alloys, and antimony trioxide. Workers were employed for at least 3 months. Cause of death of maintenance workers and zircon plant worker, and office workers at the same facility was examined as a comparison group.	**Exposure:** No monitoring data were provided. **Confounding exposure:** Investigators noted that the workers were likely exposed to arsenic in the antimony ore. Smoking status was not included as a potential confounding variable.	**Respiratory effects:** No significant increases in deaths from respiratory effects. **Cancer:** Increase in lung cancer deaths in antimony workers and maintenance workers. Only significant in workers hired prior to 1940 and between 1946 and 1950. Workers with latency period of >20 years had the highest increase in lung cancer deaths.
Kim et al. 1999	Study of 12 workers (mean age of 35 years) exposed to antimony trioxide at a manufacturing facility for an average of 30 months. Another group of 22 workers (mean age of 33 years) at the facility not near the antimony sources was also examined. A second control group of 33 volunteers (mean age of 50 years) without occupational exposure to antimony was also examined.	**Exposure:** The mean serum antimony concentration in the exposed workers was 0.766 mg/m^3. Geometric mean urine antimony concentrations were 410.8, 112.5, and 27.8 µg/g creatinine in the exposed workers, control workers, and volunteer controls, respectively. **Confounding exposure:** Co-exposure to other chemicals was likely but not discussed	**Immunological effects:** Significant decreases in serum IgG1 and IgE levels were observed in exposed workers compared to control groups. An association between IgG4 levels and urine antimony levels were found in the exposed workers; no associations were found for other IgG subgroups or for IgE. No alterations in Il-2 or interferon-gamma levels were found in the exposed workers, as compared to control workers.
Palacios et al. 2014	Linked data from the Nurses' Health Study with EPA's Air Toxic data (n=97,430 females).	**Exposure:** Median antimony concentrations for each exposure quartile were 0.000034, 0.000138, 0.000287, and 0.000682 µg/m^3. **Confounding exposure:** Co-exposure to other chemicals was likely but not discussed	**Neurological effects:** No association between antimony levels and risk of Parkinson's disease was found. Risk estimates were adjusted for age, smoking, and population density.

Table 2-1. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Potkonjak and Pavlovich 1983	51 males employed at a smelting facility. Mean duration of employment was 17.9 years (range of 9–31 years). All workers experienced pneumoconiotic changes. No control group was used.	**Exposure:** Workers were exposed to antimony oxides; 39–89% of dust was antimony trioxide and 2.1–7.8% was antimony pentoxide. No monitoring data were provided. **Confounding exposure:** Investigators noted that the airborne dust contained silica (0.82–4.72%), ferric trioxide (0.90–3.81%), and arsenic oxide (0.21–6.48%). No information on smoking was provided.	**Respiratory effects:** Clinical signs included chronic coughing (61%) and upper airway inflammation (35%). Respiratory effects included Type 1p pneumoconiosis (67%), chronic bronchitis (37%), chronic emphysema with pulmonary function changes (34%), inactive tuberculosis (18%), and pleural adhesions (28%). No consistent pattern of lung function alterations was found. **Dermal effects:** Dermatosis (63%) was found predominantly in workers exposed to excessively high temperatures. **Ocular effects:** Conjunctivitis (28%).
Renes 1953	78 males involved in smelting or employed as maintenance workers. Workers were employed for at least 2 weeks. No control group was used.	**Exposure:** Average concentrations in the breathing zone were 10.07 mg/m^3 in the furnace area and 11.81 mg/m^3 in the cupel area. **Confounding exposure:** Arsenic was present in smelting material; average levels of arsenic in the furnace and cupel areas were 1.10 and 0.36 mg/m^3, respectively. Workers were also exposed to hydrogen sulfide and iron oxide.	**Respiratory effects:** Soreness and bleeding of the nose (>70%), laryngitis (11%), and rhinitis (20%) of workers. **Gastrointestinal effects:** 11% reported gastrointestinal symptoms (abdominal cramps, diarrhea, vomiting). **Dermal effects:** Dermatitis (20%). **Neurological effects:** Nine workers reported nerve tenderness and tingling, severe headaches, and prostration. Antimony was detected in urine samples from 7/9 of these workers.

Table 2-1. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Schnorr et al. 1995	1,014 workers at an antimony smelter in Texas. Employed for at least 3 months; average length of employment was 6.8 years.	**Exposure:** Monitoring surveys conducted in 1975 and 1976 found geometric mean antimony levels of 0.5551 mg/m^3 using area samples and 0.747 mg/m^3 using personal samples. **Confounding exposure:** Investigators noted that the workers were also exposed to arsenic. Smoking status was not included as a potential confounding variable.	**Respiratory effects:** Increase in deaths from influenza (SMR=1.23) and pneumoconiosis/ other respiratory disease among workers with Spanish surnames. **Cardiovascular effects:** Increased deaths. from ischemic heart disease among Spanish surname workers as compared to a survey of Mexican-American population or to Spanish surnamed workers at a cadmium facility; the statistical significance of this finding was not reported. **Cancer:** Nonsignificant increase in deaths from lung cancer especially among workers with the longest period since first employed (>20 years) and the longest duration of employment (>10 years) (SMR=1.55; 90% CI 0.86–2.60). Significant positive trend in lung cancer deaths with increasing duration of employment when compared to an ethnic-specific rate.
Stevenson 1965	Case series of 23 workers at an antimony smelter exposed to antimony trioxide dust and reporting dermatitis.	**Exposure:** Antimony concentrations were not reported; investigators noted that most of the antimony trioxide dust was <1 µm in diameter. **Confounding exposure:** The antimony sulfide ore contained minute traces of lead, arsenic, and iron; the investigators also noted that sulfur dioxide was released during the smelting process.	**Dermal:** Erythematous papules were most commonly reported in the antecubital area and shins. The investigators noted that workers in these areas were most exposed to heat, which resulted in sweating. The rash typically subsided 3–14 days after the workers were transferred to cooler working environments.

Table 2-1. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Taylor 1966	Case series of seven workers acutely exposed to high levels of antimony trichloride.	**Exposure:** It is likely that the workers were exposed to up to 73 mg Sb/m^3. **Confounding exposure:** The workers were exposed to ≤146 mg/m^3 hydrogen chloride.	**Respiratory:** 7/7 workers reported upper respiratory tract soreness; this is likely due to the hydrogen chloride exposure. **Gastrointestinal:** Abdominal pain (4/7), vomiting (3/7), and anorexia (5/7) were reported by workers.
Wu and Chen 2017	91 workers exposed to antimony trioxide or sodium antimonite and 42 control workers at glass manufacturing and plastic product engineering facilities.	**Exposure:** Average antimony levels were 2.51, 0.14, and 0.21 mg/m^3 at the antimony trioxide production, glass manufacturing, and plastic product engineering facilities. **Confounding exposure:** Co-exposure to other chemicals was not discussed.	**Immunological:** Decreases in serum IgG, IgA, and IgE levels. Inverse correlations between immunoglobins and air antimony levels and inverse correlations between blood, urine, and hair antimony levels with IgA and IgE levels.

CI = confidence interval; EKG = electrocardiogram; EPA = Environmental Protection Agency; SMR = standardized mortality ratio

Table 2-2. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Adams et al. 2006	Children 3–15 years of age living in Arizona; 51 cases with autism spectrum disorder; 40 controls.	Mean hair antimony levels were 0.19 µg/g in cases and 0.08 µg/g in controls. Maternal hair antimony levels were 0.05 µg/g in cases and 0.04 µg/g in controls.	**Neurological effects:** No significant differences in maternal or child hair antimony levels between children with autism spectrum disorder and controls.
Adams et al. 2013	Children 5–16 years of age living in Arizona; 55 cases with autism spectrum disorder, pervasive developmental disorder, or Asperger's; 44 controls.	Mean urinary antimony levels were 0.167 µg/g creatinine in cases and 0.165 µg/g creatinine in controls.	**Neurological effects:** No association between urinary antimony levels and autism severity.
Blaurock-Busch et al. 2011	Children 3–9 years of age living in Saudi Arabia; 25 cases with autism spectrum disorder; 25 controls.	Mean hair antimony levels were 0.08 µg/g in cases and 0.07 µg/g in controls. Mean urinary antimony levels were 0.48 µg/g creatinine in cases and 0.21 µg/g creatinine in controls.	**Neurological effects:** No significant differences in hair or urine antimony levels between children with autism spectrum disorder and controls.
Bloom et al. 2015	245 infants of parents participants in the Longitudinal Investigation of Fertility and the Environment study in Michigan and Texas.	Mean maternal urinary antimony level was 0.06 µg/L (range of <0.01–0.52 µg/L); mean paternal urinary antimony level was 0.10 µg/L (range of <0.01–1.06 µg/L).	**Developmental effects:** No associations between maternal or paternal urinary antimony levels and gestational age, birth weight, birth length, head circumference, ponderal index, or newborn sex.
Colak et al. 2015	Populations living in two cities in Turkey near the Black Sea; 13,012 cancer cases were registered in 2000–2007.	541 water samples were collected from the area; antimony levels were <20 µg/L in all samples.	**Cancer effects:** A positive relationship between antimony levels and cancer incidence was found. The study examined 17 metals and found that, in total, they accounted for only 8.2% of the cancer incidence of the population.
Fido and Al-Saad 2005	Boys 4–8 years of age living in Kuwait; 40 cases with autism and 25 controls.	Median hair antimony levels were 0.08 µg/g in cases and 0.06 µg/g in controls.	**Neurological effects:** No significant differences in hair antimony levels between boys with autism and controls.

Table 2-2. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Guo et al. 2016	7,781 adults (mean age of 50.3 years) participating in the 1999–2010 NHANES.	Geometric mean urinary antimony levels were 0.08 and 0.11 µg/g creatinine among alive and deceased participants, respectively.	**Death:** Association between urinary antimony levels and all-causes mortality. **Cardiovascular effects:** No association between urinary antimony and heart disease deaths. Associations for self-reported heart disease, congestive heart failure, and heart attack. No association for self-reported angina pectoris or coronary heart disease. **Cancer:** No association between urinary antimony levels and mortalities due to malignant neoplasms. No associations with self-reported cancer.
Longerich et al. 1991	Case-control study of 28 women in Newfoundland, Canada with an infant diagnosed with neural tube defect; mothers of age-matched infants living in the same geographical region served as controls.	Mean antimony levels in drinking water were 0.02 and 0.11 ppb in the control and case groups, respectively.	**Developmental effects:** No significant difference in antimony drinking water levels between the cases and controls.
Mendy et al. 2012	1,857 adults (49.6% males, 50.4% females; mean age of 50.3 years) participating in the 2007–2008 NHANES.	Geometric mean urinary antimony level was 0.06 µg/g creatinine (95% CI 0.06–0.06).	Medical conditions were self-reported. **Respiratory effects:** No association with asthma. **Cardiovascular effects:** No associations for congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke. **Hepatic effects:** No associations with liver conditions. **Endocrine effects:** No association with thyroid conditions. **Other systemic effects:** No association with gout. **Cancer effects:** No associations with cancer.

Table 2-2. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Menke et al. 2016	9,447 adults participating in the 1999–2010 NHANES.	Not reported.	Diabetes defined as self-reported previous diagnosis or an A1C ≥6.5% (48 mmol/mol). **Other noncancer effects:** Association between urinary antimony levels and risk of diabetes. No association when evaluated in never smokers only. Association between urinary antimony and HOMA-IR among all participants and among participants without diabetes.
Navas-Acien et al. 2005	725 adults (>40 years of age) participating in the 1999–2000 NHANES.	Geometric mean urinary antimony level was 0.11 µg/L.	Peripheral arterial disease was defined as a blood pressure ankle brachial index <0.9 in at least one leg. **Cardiovascular effects:** No association between urinary antimony levels and peripheral arterial disease.
Scinicariello et al. 2017	2,654 adults aged ≥20 years participating in 2005–2008 NHANES.	Geometric mean urinary antimony level was 0.06 µg/L.	Medical conditions were self-reported. **Neurological effects:** Associations between urinary antimony levels and insufficient sleep (≤6 hours/night) and prolonged sleep-onset latency to fall asleep (more than 30 minutes per night). Obstructive sleep apnea, sleep problems, and day-time sleepiness associated with antimony levels above the reference value of 0.03 µg/L.

Table 2-2. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Shiue 2014	5,864 adults aged ≥20 years participating in 2011–2012 NHANES.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	High blood pressure (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg) was found in 31.1% of the total population (this rate includes children, which were not included in the statistical analyses); blood pressure classification was based on a single blood pressure measurement. **Cardiovascular effects:** Association between urinary antimony levels and high blood pressure; OR of 1.56 (95% CI 1.29–1.89) with adjusting for urine creatinine levels, age, sex, body mass index, and ratio of family income to poverty level. In weighted model (also includes adjustment for subsample weighting), the OR was 1.39 (95% CI 1.10–1.77). The study also found associations for several other metals (cobalt, cesium, manganese, lead, tin, platinum, molybdenum, thallium, and tungsten).
Shiue 2015	5,031 adults (48.4% males, 51.6% females) aged 20-–9 years participating in 2009–2010 NHANES; the mean age was 44 years.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	Ankylosing spondylitis was assessed via clinical measures of occiput-to-wall distance and chest expansion; values of >2 and >2.5 cm were considered abnormal; active lumbar flexion was also used to assess ankylosing spondylitis but the criterion was not reported. **Musculoskeletal effects:** Association between urinary antimony levels and occiput-to-wall distance; OR of 1.74 (95% CI 1.15–2.62). No association with chest expansion (OR 0.90; 95% CI 1.65–1.29) or active lumbar flexion (OR -0.05; 95% CI -0.17–0.03).

Table 2-2. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Shiue and Hristova 2014	Adults aged ≥20 years participating in 2009–2012 NHANES; based on data presented in the paper, 2,391 participants were ≥18 years for age.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	See Shiue (2014) for blood pressure criteria. **Cardiovascular effects:** Association between urinary antimony levels and high blood pressure; OR of 1.99 (95% CI 1.30–1.95) with adjusting for urine creatinine levels, age, sex, body mass index, and ratio of family income to poverty level. In weighted model (also includes adjustment for subsample weighting), the OR was 1.44 (95% CI 1.12–1.86). The investigators estimated that antimony accounted for 6.2% of the population risk.
Vigeh et al. 2017	174 children aged 20–36 months.	Mean hair antimony levels were 0.102 and 0.188 µg/g in boys and girls, respectively.	**Body weight:** No significant differences in hair antimony levels between children weighing less than the 50th percentile at 18 months of age and those weighing more than the 50th percentile.
Wang et al. 2016	1,247 male partners from sub-fertile couples attending a reproductive clinic in China.	Median urinary antimony level was 0.17 µg/L.	**Reproductive effects:** No associations between urinary antimony levels and reproductive hormone levels (estradiol, FSH, LH, testosterone, SHBG), sperm apoptosis parameters, or sperm DNA damage
Zheng et al. 2014	1,106 women in China	Umbilical cord antimony was measured.	**Developmental effects:** Median umbilical cord antimony was significantly higher in women with adverse pregnancy outcomes (18.6 µg/L) compared to controls (0.16 µg/L); however, the risk of adverse pregnancy outcome in association with antimony was not statistically significant.

CI = confidence interval; FSH = follicle stimulating hormone; HOMA-IR = homeostatic model assessment of insulin resistance; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; SHBG = sex hormone-binding globulin

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M, 5 F	30 minutes	0, 122, 799, 1,395	CS, BW, GN, HP	Death			1,395	Increased mortality (7/10) at an unspecified time post-exposure
					Resp	122	1,395		Pulmonary edema and congestion
					Cardio	122			
					Hepatic	122			
					Renal	122			
					Endocr	122			
Stibine NIOSH 1979									
2	Rat (Wistar) 5 M, 5 F	16 days 6 hours/day, 5 days/week	0, 3.1, 6.3, 12, 25, 50	CS, BW, OW, GN, HP	Bd wt	50			
					Resp	12	25		Chronic inflammation in the lungs and squamous metaplasia in the epiglottis
Antimony trioxide NTP 2016									
3	Mouse (B6C3F1) 5 M, 5 F	17 days, 6 hours/day, 5 days/week	0, 3.1, 6.3, 12, 25, 50	CS, BW, OW, GN, HP	Bd wt	50			
					Resp	6.3	12[b]		Squamous metaplasia in epiglottis epithelium at 12 mg Sb/m^3; increases in relative lung weights at 3.1 mg Sb/m^3
Antimony trioxide NTP 2016									
4	Guinea pig (Hartley) 5 M,5 F	30 minutes	0, 122, 799, 1,395	CS, BW, GN, HP	Death			1,395	
					Resp	799	1,395		Pulmonary edema and congestion
					Renal	122	799		Renal tubular dilation in 3/10 animals
Stibine NIOSH 1979									

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
5	Rabbit (NS) 5 NS	5 days, 7 hours/day	0, 19.9	LE, OF, HP	Resp		19.9		Lung inflammation
					Cardio		19.9		Degenerative changes in heart; EKG alterations
					Hepatic		19.9		Degenerative liver lesions
					Renal		19.9		Degenerative kidney lesions
Antimony trisulfide Brieger et al. 1954									
INTERMEDIATE EXPOSURE									
6	Rat (NS) 10-24 F	1.5–2 months, 4 hours/day	0, 209	BW, GN, HP, MX, DX	Bd wt	209			
					Resp		209		Unspecified pathological changes in the lungs
					Hepatic		209		Unspecified pathological changes in the liver
					Renal		209		Unspecified pathological changes in the kidneys
					Endocr		209		Unspecified pathological changes in the pancreas
					Repro		209		Reduced fertility and unspecified histological alterations in reproductive organs
					Develop		209		Reduced litter size; not specified whether due to pre-implantation loss or post-implantation loss
Antimony trioxide Belyaeva 1967									
7	Rat (Wistar) 10 M	6 weeks, 7 hours/day 5 days/week	0, 2.20	LE, CS, BW, OF, GN, HP	Bd wt	2.2			
					Resp		2.2		Mild congestion and focal hemorrhages in the lungs
					Cardio		2.2		Altered EKG and microscopic changes in heart muscle consistent with degeneration of the myocardium
Antimony trisulfide Brieger et al. 1954									

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
8	Rat (Fischer-344) 50 M, 50 F	13 weeks, 6 hours/day, 5 days/week	0, 0.21, 0.902, 4.11, 19.60	CS, BW, OP, HE, BI, HP	Bd wt	19.6			
					Resp	0.902	4.11		Increases in alveolar/ intra-alveolar macrophages, relative lung weight, and in lung clearance half-times at ≥4.11 mg Sb/m^3; chronic interstitial inflammation and fibrosis at 19.60 mg Sb/m^3 at the end of a 27-week recovery period
					Cardio	19.6			
					Hemato	19.6			
Antimony trioxide Newton et al. 1994									
9	Guinea pig (NS) 24 NR	32 weeks, 2 hours/day, 7 days/week for 2 weeks and 3 hours/day, 7 days/week for 30 weeks	0, 37.9	CS, BW, HE, OF, HP	Bd wt	37.9			
					Resp		37.9		Pneumonitis
					Hemato		37.9		Decreases in total and differential leukocyte counts
					Hepatic		37.9		Fatty degeneration in the liver
					Immuno		37.9		Hypertrophy of lymphoid follicles in the spleen
Antimony trioxide Dernehl et al. 1945									
10	Dog (NS) 2 F	7 weeks, 7 hours/day 5 days/week	0, 3.81	LE, CS, BW, HE, BI	Bd wt	3.81			
					Cardio	3.81			
					Hemato	3.81			
Antimony trisulfide Brieger et al. 1954									

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
11	Dog (NS) 2F	10 weeks, 7 hours/day, 5 days/week	0, 3.98	LE, CS, BW, HE, BI	Bd wt	3.98			
					Cardio		3.98		EKG alterations indicative of myocardial injury; occasional swelling of myocardial fibers
					Hemato	3.98			
Antimony trisulfide Brieger et al. 1954									
12	Rabbit (NS) 6M	6 weeks, 7 hours/day, 5 days/week	0, 4.02	LE, HE, BI, OF, GN, HP	Cardio		4.02 M		Altered EKG, heart enlargement, swelling of myocardial fibers; only qualitative data were presented
					Hemato	4.02			
					Hepatic	4.02			
					Renal	4.02			
Antimony trisulfide Brieger et al. 1954									
CHRONIC EXPOSURE									
13	Rat (Sprague-Dawley) 50 M	14.5 months, 25 hours/week	0.2, 84–105	GN, HP	Resp		84 M		Gross and microscopic alterations in the lungs consistent with lipoid pneumonia
Antimony trisulfide Gross et al. 1952									
14	Rat (Wistar) 90 M, 90 F	52 weeks, 7 hours/day, 5 days/week	0, 36	LE, CS, BW, GN, HP	Bd wt	36			
					Resp		36		Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia persisting months after exposure ceased.
					Cardio	36			
					Hepatic	36			
					Renal	36			
					Dermal	36			
					Endocr	36			
					Immuno	36			
					Neuro	36			

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
					Repro	36			
					Other noncancer	36			
					Cancer			36 F	Lung neoplasms
Antimony trioxide Groth et al. 1986									
15	Rat (Wistar) 90 M, 90 F	52 weeks, 7 hours/day, 5 days/week	0, 17.5	LE, CS, BW, GN, HP	Bd wt	17.5			
					Resp		17.5		Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia persisting months after exposure ceased
					Cardio	17.5			
					Gastro	17.5			
					Hepatic	17.5			
					Renal	17.5			
					Dermal	17.5			
					Ocular	17.5			
					Endocr	17.5			
					Immuno		17.5		Mononuclear cell granulomas in tracheobronchial lymph nodes
					Repro	17.5			
					Other noncancer	17.5			
					Cancer			17.5 F	Lung neoplasms
Antimony Groth et al. 1986									

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
16	Rat (Fischer-344) 65 M, 65 F	12 months, 6 hours/day, 5 days/week	0, 0.05, 0.43, 3.8	CS, BW, OP, HE, BC, HP	Bd wt	3.8			
					Resp	0.05	0.43[c]		Increase in alveolar/intra-alveolar macrophages at ≥0.05 mg Sb/m^3 at the end of the exposure period and 12-month recovery period; increase in chronic interstitial inflammation ≥0.43 mg Sb/m^3 in rats killed during the recovery period; decreases in lung clearance (40 and 80%) at 0.43 and 3.8 mg Sb/m^3
					Hemato	3.8			
					Ocular	0.05	0.43		Moderate or severe lenticular degeneration
					Immuno	0.43	3.8		Reticuloendothelial cell hyperplasia in peribronchiolar lymph nodes
Antimony trioxide Newton et al. 1994									
17	Rat (Wistar) 50 M, 50 F	2 years, 6 hours/day, 5 days/week	0, 2.5, 8.3, 25	CS, LE, BW, GN, HP	Death			8.3	Decreased survival in females and decreased survival trend in males
					Bd wt	2.5 F	8.3 F		Decreases in body weight gain in females at 2.5 (10%), 8.3 (20%), and 25 (28%) mg Sb/m^3 and in males at 25 mg Sb/m^3 (20%)
					Resp		2.5		Inflammation, proteinosis, hyperplasia, and fibrosis at ≥2.5 mg Sb/m^3; hyperplasia of nasal respiratory epithelium at 2.5 mg Sb/m^3 (males only) and 25 mg Sb/m^3 (males and females) and squamous metaplasia of nasal epithelium in males at 25 mg Sb/m^3
					Cardio	2.5 F	8.3 F		Chronic inflammation of muscular arteries at 8.3 (females only) and 25 mg Sb/m^3
					Gastro	8.3			
					Musc/skel	8.3	25		Bone marrow hyperplasia
					Hepatic	25			

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
					Renal	2.5 F	8.3 F		Hyaline droplet accumulation at 8.3 (females only) and 25 mg Sb/m^3 and nephropathy in females at 25 mg Sb/m^3
					Ocular		2.5 F		Ciliary body inflammation at 25 mg Sb/m^3 and retinal atrophy in females at ≥2.5 mg Sb/m^3
					Endocr	25			
					Immuno		2.5		Lymphoid hyperplasia in bronchial and mediastinal lymph nodes
					Neuro	25			
					Repro		2.5 M		Epithelial hyperplasia of the prostate gland at 2.5 and 8.3 mg Sb/m^3; increases in severity were observed in all antimony exposed groups
					Other noncancer	25			
					Cancer			8.3 F	Alveolar/bronchiolar adenomas in females at ≥8.3 mg Sb/m^3, benign pheochromocytoma in adrenal medulla at 25 mg Sb/m^3 and combined incidence of benign and malignant pheochromocytomas in females at 25 mg Sb/m^3
Antimony trioxide NTP 2016									
18	Rat (Fischer-344) 49–50 F	55 weeks, 6 hours/day, 5 days/week	0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP	Resp		1.6		Focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumocyte hyperplasia, and pigmented macrophages in the lungs
					Cardio	4.2			
					Gastro	4.2			
					Hemato	4.2			

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
					Musc/skel	4.2			
					Hepatic	4.2			
					Renal	4.2			
					Endocr	4.2			
					Immuno	4.2			
					Neuro	4.2			
					Repro	4.2			
					Other noncancer	4.2			
					Cancer			4.2	Lung neoplasms
Antimony trioxide Watt 1983									
19	Mouse (B6C3F1) 50 M, 50 F	2 years, 6 hours/day, 5 days/week	0, 2.5, 8.3, 25	CS, LE, BW, GN, HP	Death			8.3	Decreased survival
					Bd wt	2.5 M	8.3 M		Decreases in body weight gain in males at 8.3 and 25 mg Sb/m^3 (11 and 25%) and in females at 25 mg Sb/m^3 (21%).
					Resp		2.5		Chronic, inflammation, fibrosis (alveolus and pleural), and alveolar and bronchiolar epithelial hyperplasia at ≥2.5 mg Sb/m^3; laryngeal respiratory epithelial hyperplasia was observed at ≥8.3 mg Sb/m^3; squamous metaplasia of nasal respiratory epithelium in females at 25 mg Sb/m^3; and epithelial hyperplasia in the trachea of males exposed to 25 mg Sb/m^3
					Cardio	2.5	8.3		Chronic inflammation of epicardium
					Gastro	8.3 M	25 M		Chronic active inflammation in the forestomach of males
					Hemato	8.3 F	25 F		Hematopoietic cell proliferation in the spleen in females
					Musc/skel		2.5		Bone marrow hyperplasia

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
					Hepatic	25			
					Renal	25			
					Endocr	25			
					Immuno		2.5		Lymphoid hyperplasia in the bronchial and mediastinal (males only) lymph nodes and thymic cellular depletion
					Neuro	25			
					Repro	25			
					Other noncancer	25			
					Cancer			2.5	Increased incidences of alveolar/ bronchiolar adenomas, carcinomas, or combined at ≥2.5 mg Sb/m^3; other neoplastic lesions included malignant lymphoma in females at ≥2.5 mg Sb/m^3 and fibrous histiocytoma in the skin in males at 25 mg Sb/m^3
Antimony trioxide									
NTP 2016									
20	Pig (Sinclair S-1 miniature) 2-3 F	55 weeks, 6 hours/day, 5 days/week	0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP	Bd wt	4.2			
					Resp	4.2			
					Cardio	4.2			
					Gastro	4.2			
					Hemato	4.2			
					Hepatic	4.2			
					Renal	4.2			
					Endocr	4.2			
					Immuno	4.2			

Table 2-3. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/m^3)	Parameters monitored	Endpoint	NOAEL (mg Sb/m^3)	Less serious LOAEL (mg Sb/m^3)	Serious LOAEL (mg Sb/m^3)	Effects
					Neuro	4.2			
					Repro	4.2			
					Other noncancer	4.2			
Antimony trioxide									
Watt 1983									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an acute-duration inhalation minimal risk level (MRL) for antimony; based on a $BMCL_{HEC}$ of 0.035 mg Sb/m^3 and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive a chronic-duration inhalation MRL for antimony; based on a $BMCL_{HEC}$ of 0.008 mg Sb/m^3 and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BMDL = 95% lower confidence limit on the benchmark dose; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; EKG = electrocardiogram; F = female(s); Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight Repro = reproductive; Resp = respiratory; Sb = antimony

Figure 2-2. Levels of Significant Exposure to Antimony – Inhalation

Acute (≤14 days)

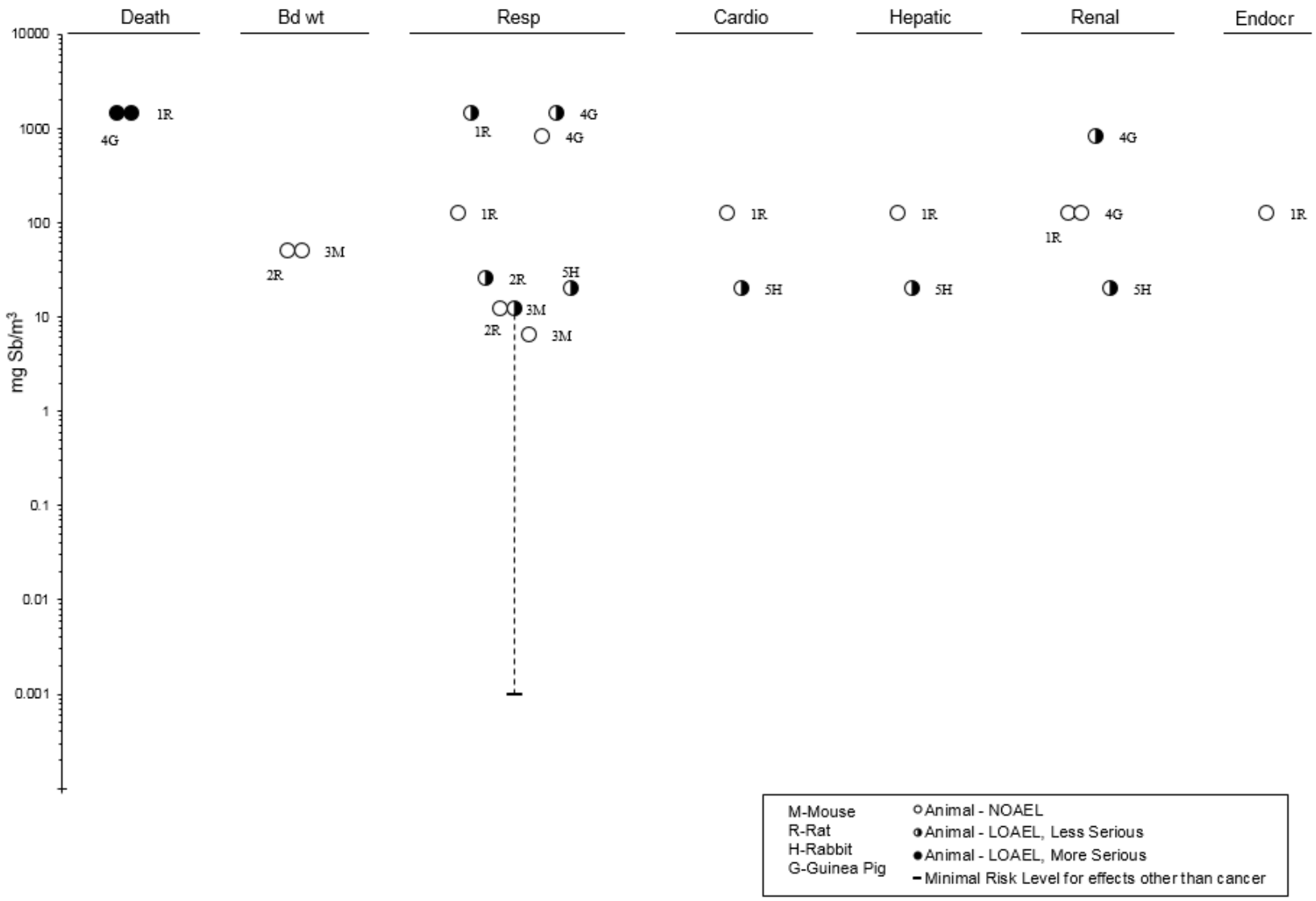


Figure 2-2. Levels of Significant Exposure to Antimony – Inhalation

Intermediate (15-364 days)

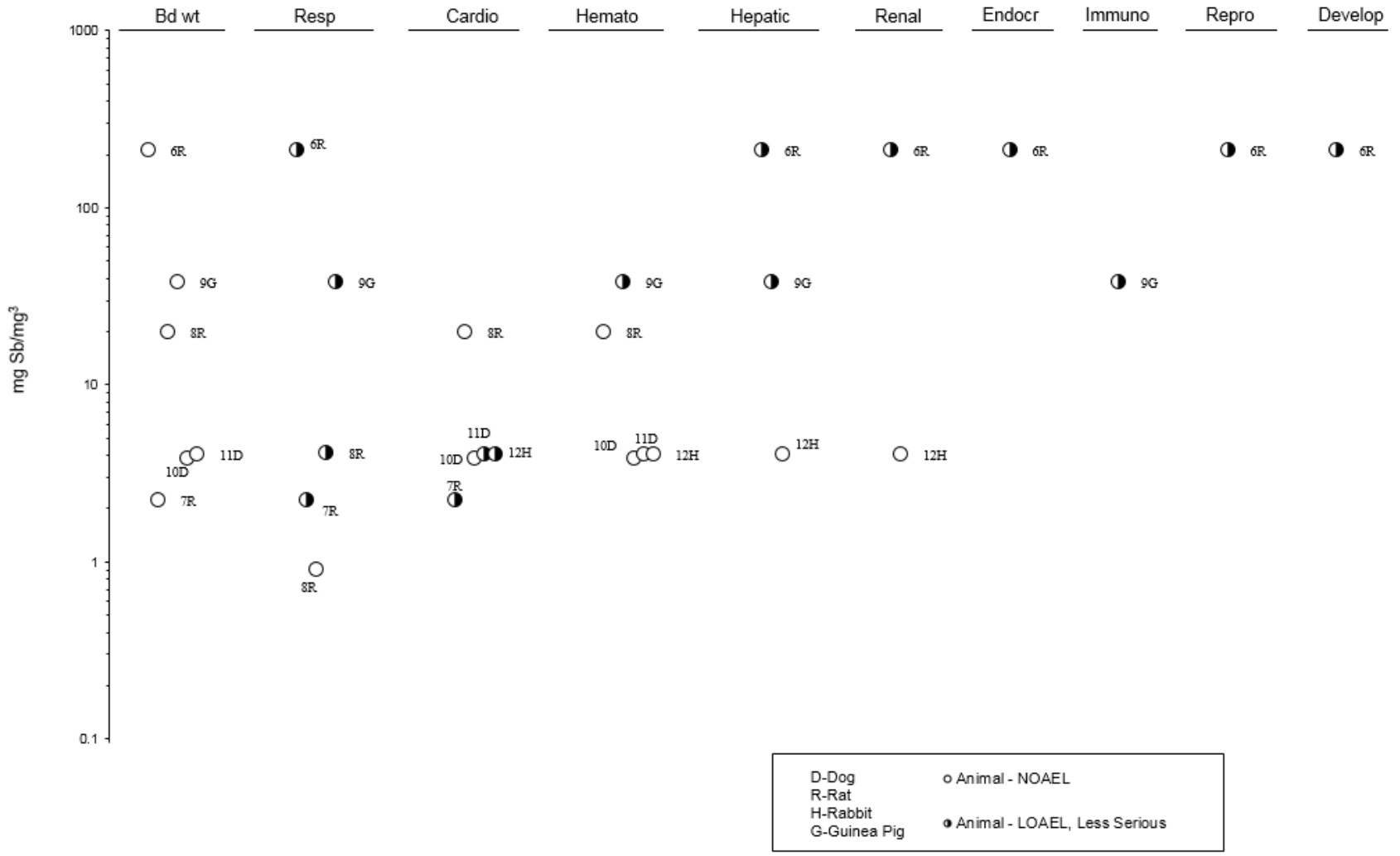


Figure 2-2. Levels of Significant Exposure to Antimony – Inhalation

Chronic (≥365 days)

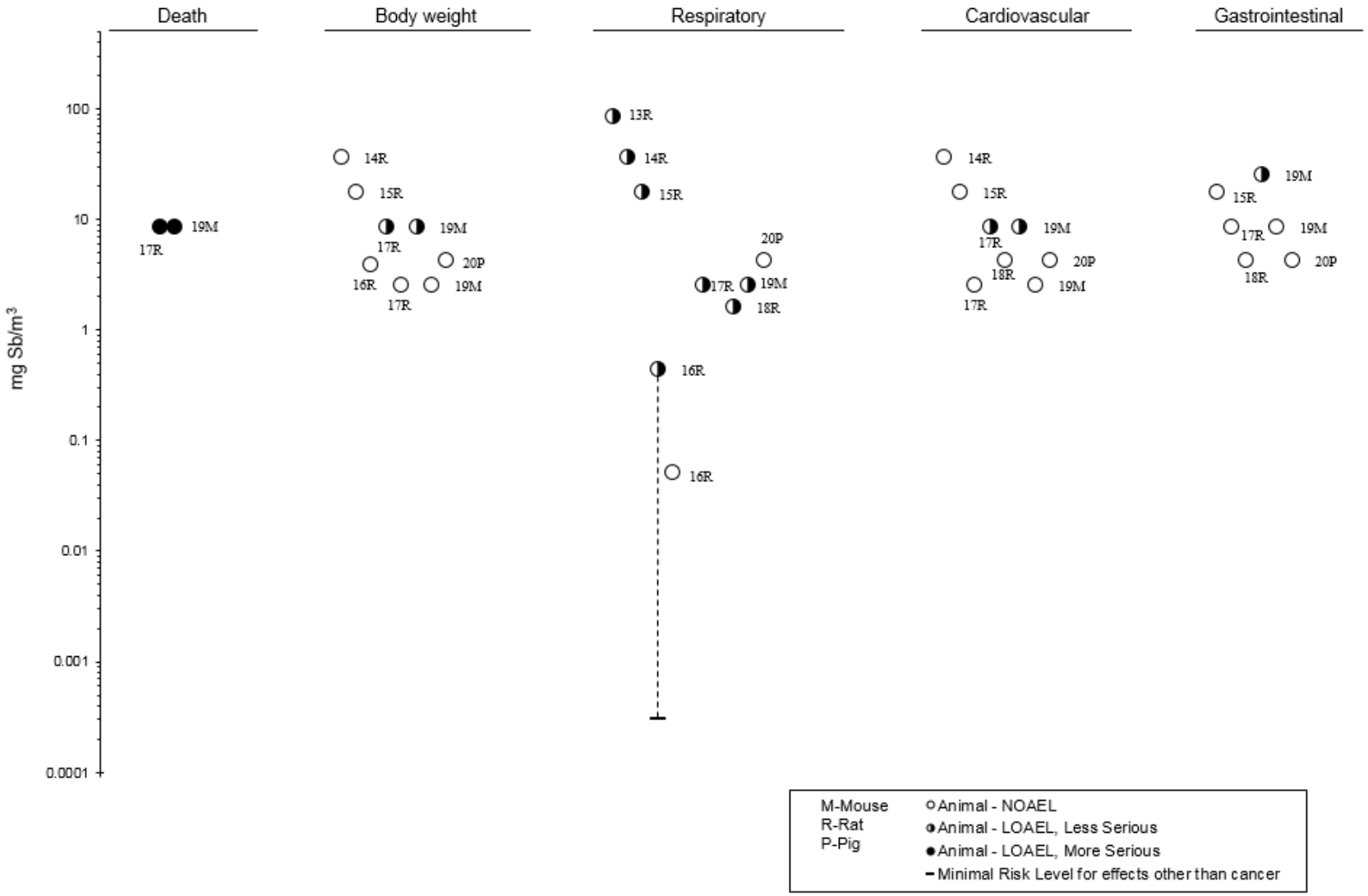


Figure 2-2. Levels of Significant Exposure to Antimony – Inhalation

Chronic (≥365 days)

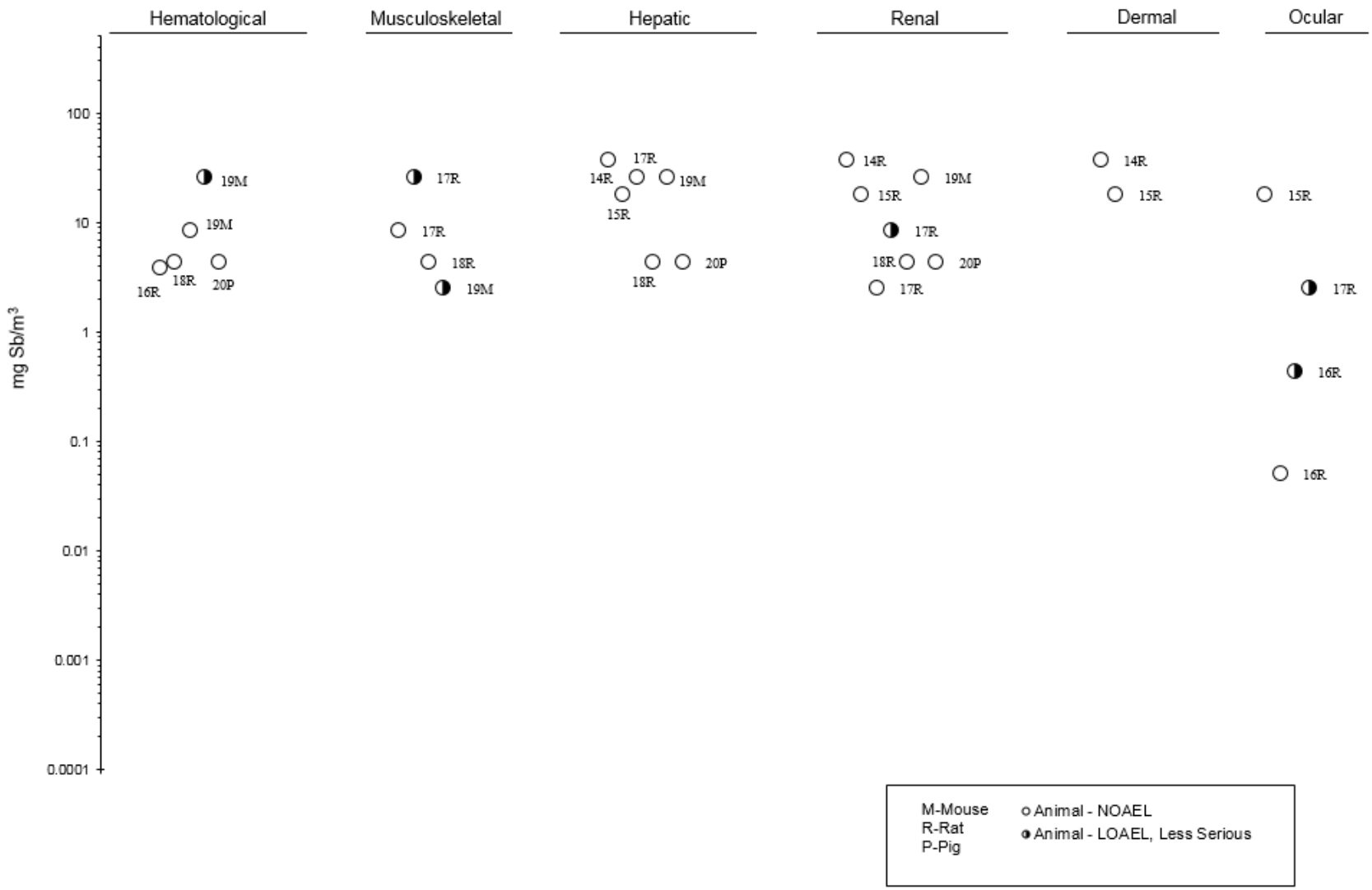


Figure 2-2. Levels of Significant Exposure to Antimony – Inhalation

Chronic (≥365 days)

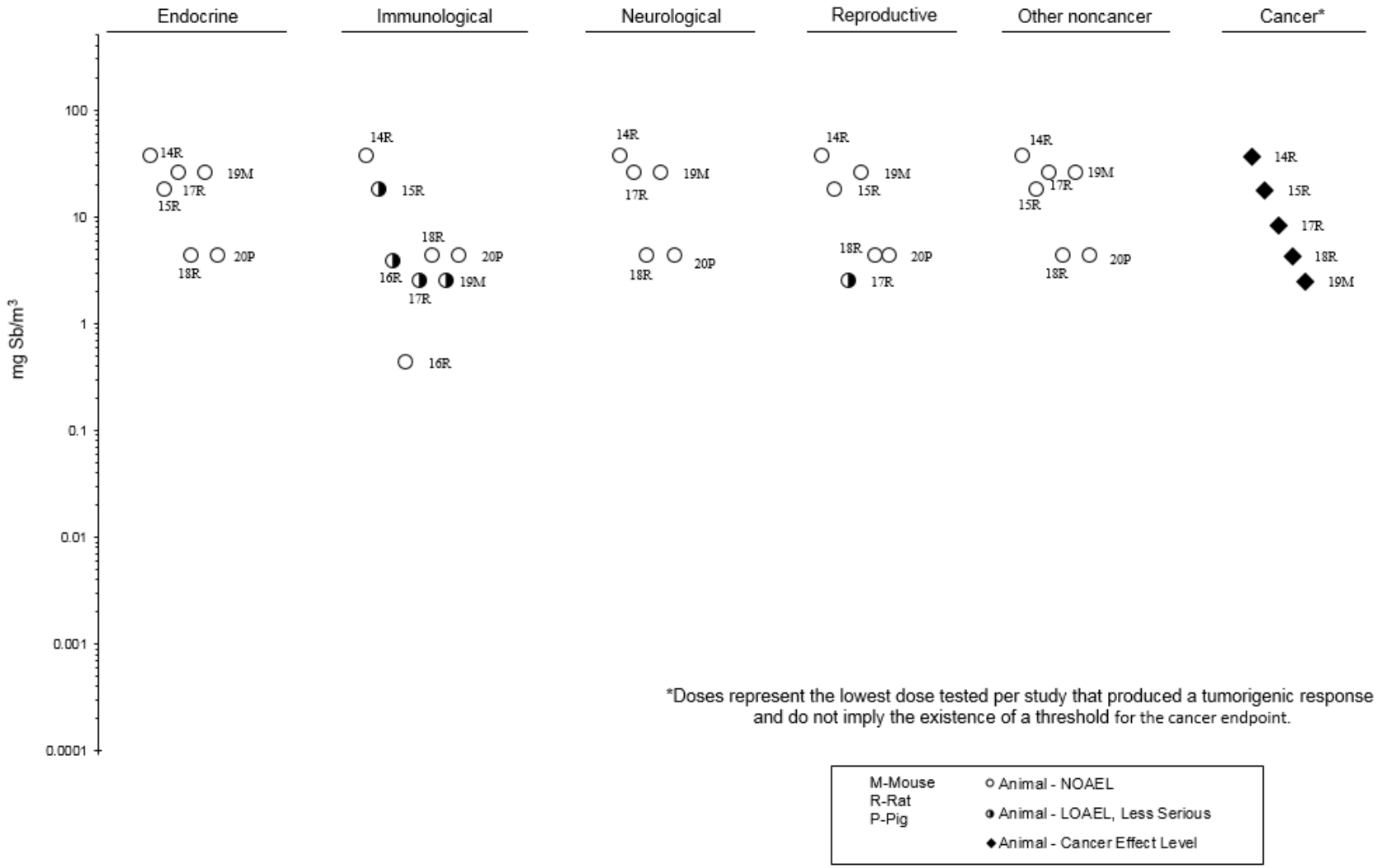


Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
ACUTE EXPOSURE									
1	Rat (Fischer-344) 10 M, 10 F	14 days (W)	0, 5.8, 10, 21, 34, 61	BW, WI, CS, OW, HP	Bd wt	61			
					Resp	61			
					Cardio	61			
					Gastro	61			
					Musc/skel	61			
					Hepatic	61			
					Renal	61			
					Endocr	61			
Antimony potassium tartrate NTP 1992									
2	Mouse (B6C3F1) 10 M, 10 F	14 days (W)	0, 21, 36, 63, 99, 150	BW, WI, CS, OW, HP	Bd wt	63	99		Decreased body weight gain was observed at ≥99 mg Sb/kg/day midway through the study; terminal body weights were within 93% of controls
					Resp	150			
					Cardio	150			
					Gastro	99	150		Focal ulceration in the forestomach
					Hepatic	99[b]	150		Minimal-to-moderate hepatocellular cytoplasmic vacuolization
					Endocr	150			
Antimony potassium tartrate NTP 1992									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
3	Dog (Beagle) 13 M, F	Once (W)	4.8	CS	Gastro		4.8		Vomiting
Antimony potassium tartrate Houpt et al. 1984									
INTERMEDIATE EXPOSURE									
4	Rat (NS) 30 F	22 days (W)	0, 0.07, 0.8	BW, OF	Bd wt	0.8			
					Cardio	0.8			
Antimony trichloride Angrisani 1988; Marmo et al. 1987									
5	Rat (NS) 10 M, F	38 days (W)	0, 0.1, 1	BW, OF	Bd wt	1			
					Cardio		0.1		Altered vasomotor response to 1-noreadrenaline and 1-isoprenaline in pups
Antimony trichloride Angrisani 1988; Marmo et al. 1987									
6	Rat (Wistar) 12 M, 1 2F	90 days (F)	M: 0, 70, 353, 1,408; F: 0, 81, 413, 1,570	CS, OP, BW, FI, UR, HE, BC, OW, HP	Bd wt	1,408			
					Resp	1,408			
					Cardio	1,408			
					Gastro	1,408			
					Hemato	1,408			
					Musc/skel	1,408			
					Hepatic	1,408			
					Renal	1,408			
					Ocular	1,408			
					Endocr	1,408			
Antimony trioxide Hext et al. 1999									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
7	Rat (Wistar) 12 M	12 weeks (F)	0, 700	CS, BW, OW, HE, BC	Bd wt	700			
					Hemato	700			
Antimony trioxide Hiraoka 1986									
8	Rat (Wistar) 12 M	12 weeks (F)	0, 85, 850	CS, BW, OW, HE, BC	Bd wt		85		Decrease in body weight gain (10% at 85 mg Sb/kg/day and 18% at 850 mg Sb/kg/day)
					Hemato	850			
Antimony Hiraoka 1986									
9	Rat (NS) 30 F	44 days (W)	0, 0.07, 0.7	BW, OF	Bd wt	0.07	0.7		11% decrease in body weight gain
					Cardio	0.7			
Antimony trichloride Marmo et al. 1987; Rossi et al. 1987									
10	Rat (Wistar) 7–8 M	4 weeks, 3 days/week (G)	0, 10, 1,000	OW, HP	Repro	1,000			
Antimony trioxide Omura et al. 2002									
11	Rat (Wistar) 8 M	4 weeks, 3 days/week (G)	0, 10	OW, HP	Repro	10			
Antimony potassium tartrate Omura et al. 2002									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
12	Rat (Sprague-Dawley) 15 M, 15 F	13 weeks (W)	M: 0, 0.06, 0.56, 5.58, 42.17; F: 0, 0.06, 0.64, 6.13, 45.69	BW, FI, WI, HE, BI, OW, HP	Bd wt	42.17			
					Resp	42.17			
					Cardio	42.17			
					Gastro	42.17			
					Hemato	5.58 M	42.17 M		5% decrease in red blood cell levels and 12% decrease in platelet counts
					Hepatic	42.17			
					Renal	42.17			
					Dermal	42.17			
					Endocr	42.17			
					Immuno	0.06 M	0.56 M		Increase in medullary volume in thymus gland in males at ≥0.56 mg Sb/kg/day and females at ≥6.13 mg Sb/kg/day
					Other noncancer	0.56	5.58		Mild sinus congestion in spleen at ≥0.56 mg Sb/kg/day (males); hyperplasia at ≥0.64 mg Sb/kg/day (females) and at 42.17 mg Sb/kg/day (males)
					Other noncancer	0.06 F[c]	0.64 F		Decreases in serum glucose levels (15–17%)
Antimony potassium tartrate Poon et al. 1998									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
13	Rat (NS) 10 M, F	38 days (W)	0, 0.1, 1	BW, OF	Develop		0.1		Significant alterations in vasomotor response to 1-noradrenaline and 1 isoprenaline at ≥0.1 mg Sb/kg/day at 60 days of age and to acetylcholine at 1 mg Sb/kg/day at 60 days of age
Antimony trichloride Rossi et al. 1987; Marmo et al. 1987									
14	Rat (NS) 30 F	44 days (W)	0, 0.07, 0.7	BW, CS, MX, DX	Develop	0.07	0.7		Decreased pup growth on PNDs10–60; pups weighed 26 and 47% less than controls on PNDs 10 and 22, respectively
Antimony trichloride Rossi et al. 1987									
15	Rat (NS) 10 M	30 days (F)	0, 50, 230, 890	BW, OW, HE	Hemato	230	890		Significantly increased (21%) red blood cell count.
					Renal	890			
Antimony trioxide Smyth and Thompson 1945									
16	Rat (Wistar) 5 M	24 weeks (F)	0, 620, 1,200	CS, BW, FI, WI, OW, HE, BI, HP	Bd wt	1,200			
					Hemato		620		Reduced red blood cell count
					Hepatic		620		Cloudy swelling in hepatic cords at 620 (3/5) and 1,200 (2/5) mg Sb/kg/day
Antimony trioxide Sunagawa 1981									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
17	Rat (Wistar) 5 M	24 weeks (F)	0, 370, 740, 1,500	CS, BW, FI, WI, OW, HE, BI, HP	Bd wt	740	1,500		Decreased terminal body weight
					Hemato	740	1,500		Decreased hematocrit and hemoglobin
					Hepatic	370	740		Increased incidence of disorder of the hepatic cords
Antimony Sunagawa 1981									
18	Mouse (CD) 9–10 M	4 weeks, 5 days/week (G)	0, 10, 1,000	OW, HP	Repro	1,000			
Antimony trioxide Omura et al. 2002									
19	Mouse (CD) 10 M	4 weeks, 5 days/week (G)	0, 10	OW, HP	Repro	10			
Antimony potassium tartrate Omura et al. 2002									
CHRONIC EXPOSURE									
20	Rat (Long-Evans) 50–60 M, 50–60 F	Lifetime (W)	0, 0.63	LE, BW, OW, UR, GN	Death			0.63	Reduced survival rate in male and female rats; at the median life spans, males survived 106 days and females 107 days less than controls
					Bd wt	0.63			
					Cardio	0.63			
					Other noncancer		0.63		Decreased (28–30%) non-fasting serum glucose
Antimony potassium tartrate Schroeder et al. 1970									

Table 2-4. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg Sb/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Sb/kg/day)	Less serious LOAEL (mg Sb/kg/day)	Serious LOAEL (mg Sb/kg/day)	Effects
21	Mouse (CD-1) 54 M, 54 F	Lifetime (W)	0, 0.35	LE, BW, HP	Death			0.35 F	Decreased survival
					Bd wt	0.35			
					Hepatic	0.35			
Antimony potassium tartrate Kanisawa and Schroeder 1969									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an acute-duration oral minimal risk level (MRL) for antimony; based on a NOAEL of 99 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration oral MRL for antimony; based on a NOAEL of 0.06 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage-not specified; (GO) = gavage-oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OP = ophthalmology; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; Sb = antimony; UR= urinalysis; (W) = drinking water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Antimony – Oral

Acute (≤14 days)

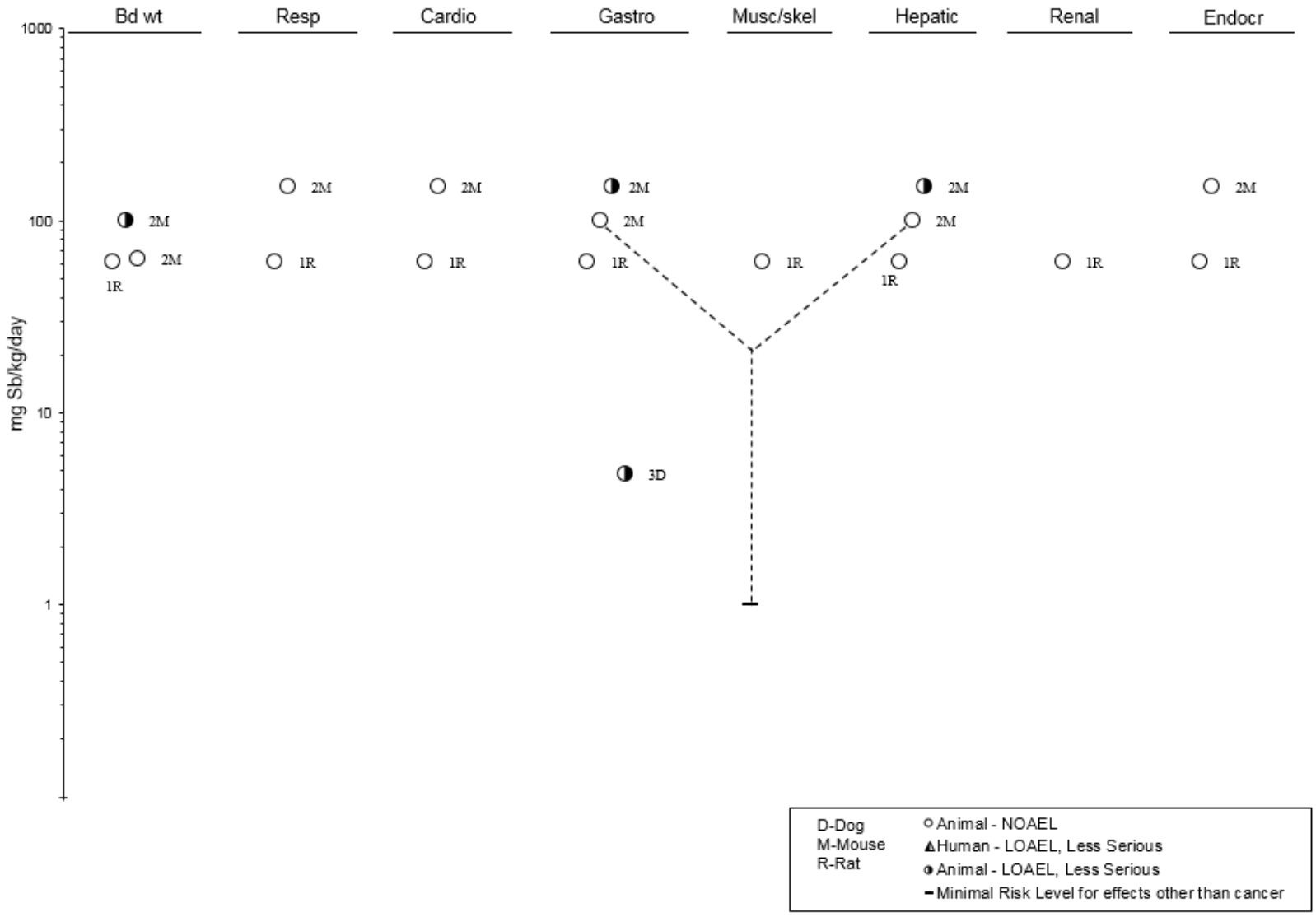


Figure 2-3. Levels of Significant Exposure to Antimony – Oral

Intermediate (15-364 days)

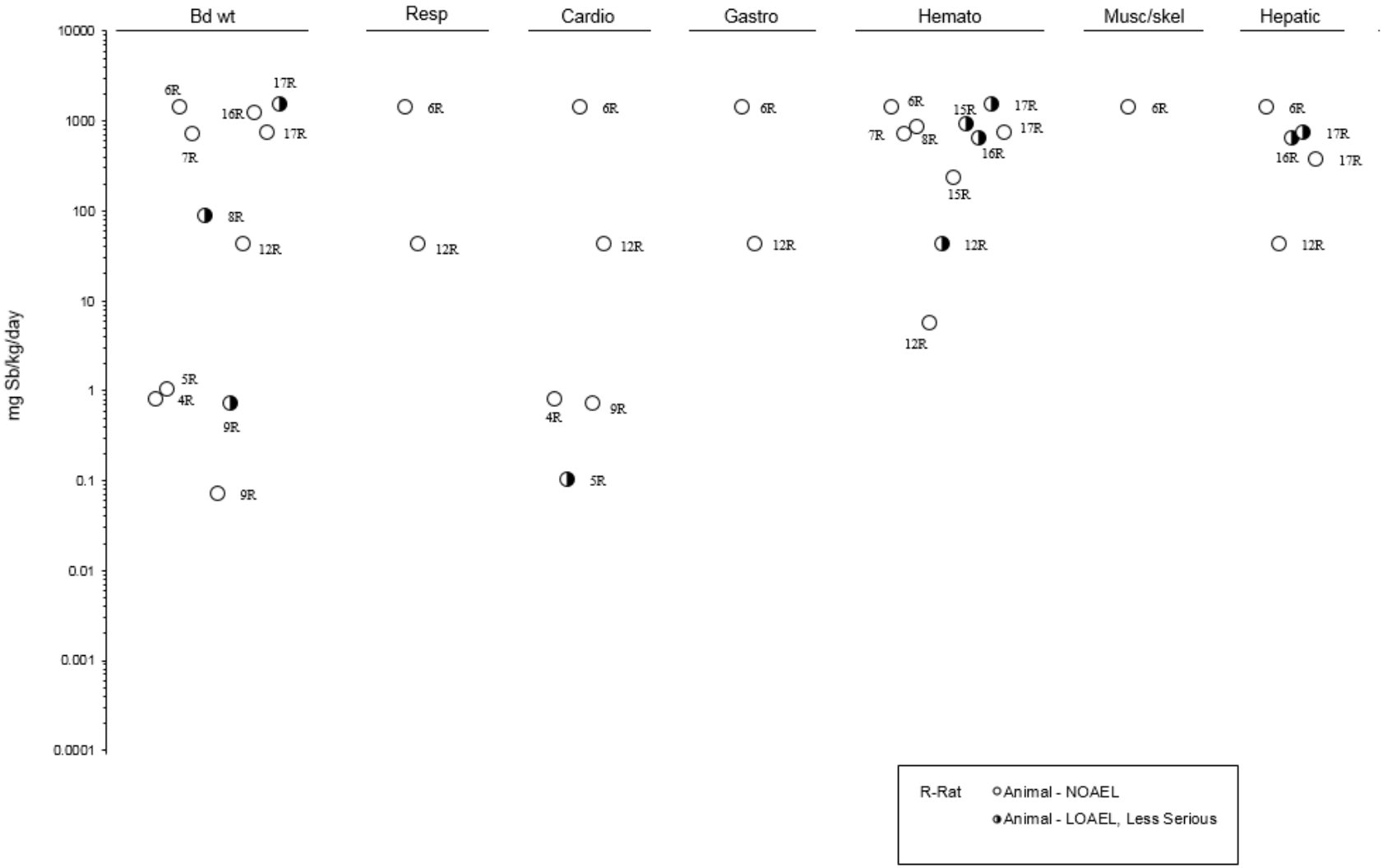


Figure 2-3. Levels of Significant Exposure to Antimony – Oral

Intermediate (15-364 days)

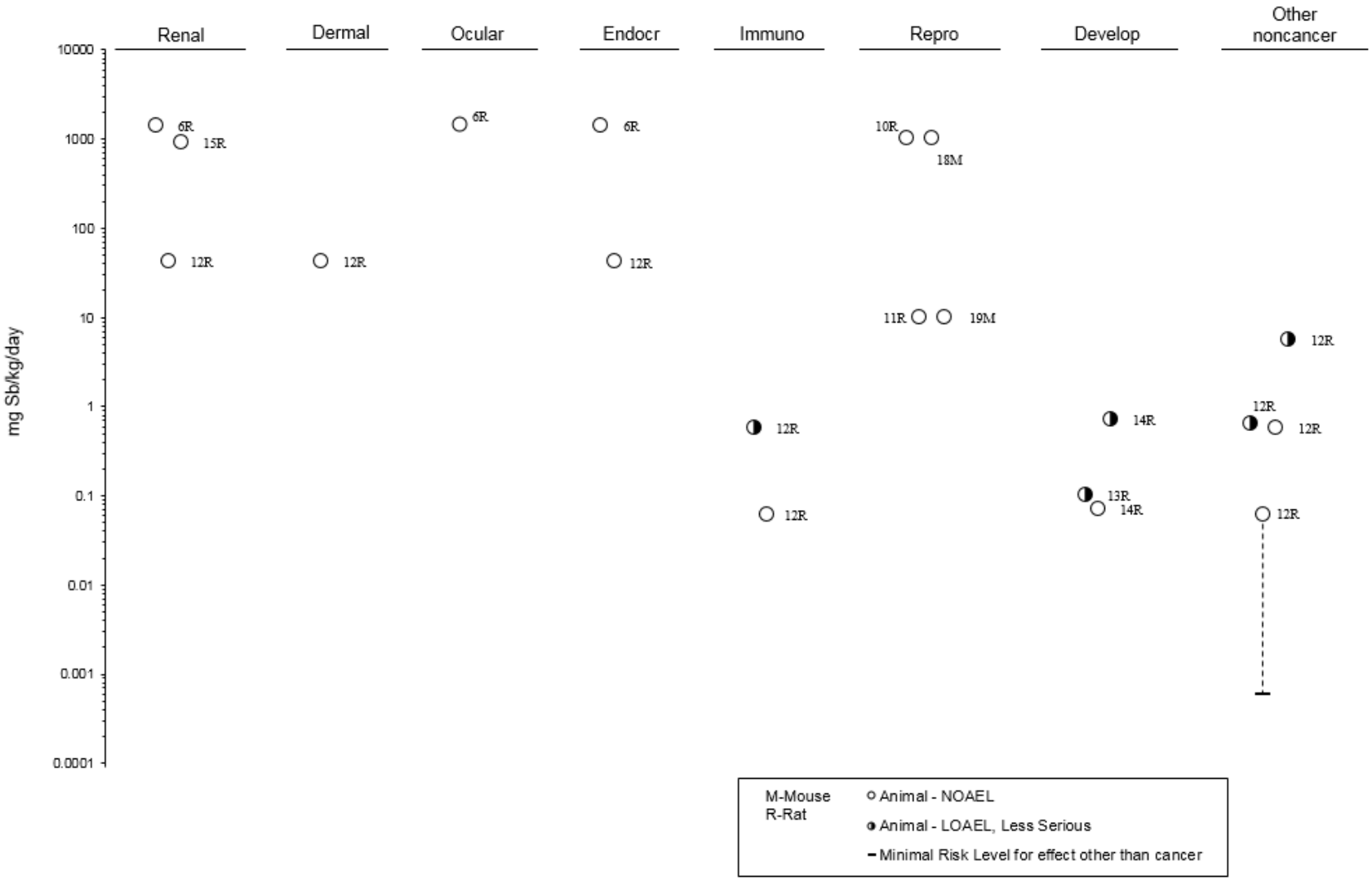


Figure 2-3. Levels of Significant Exposure to Antimony – Oral

Chronic (≥365 days)

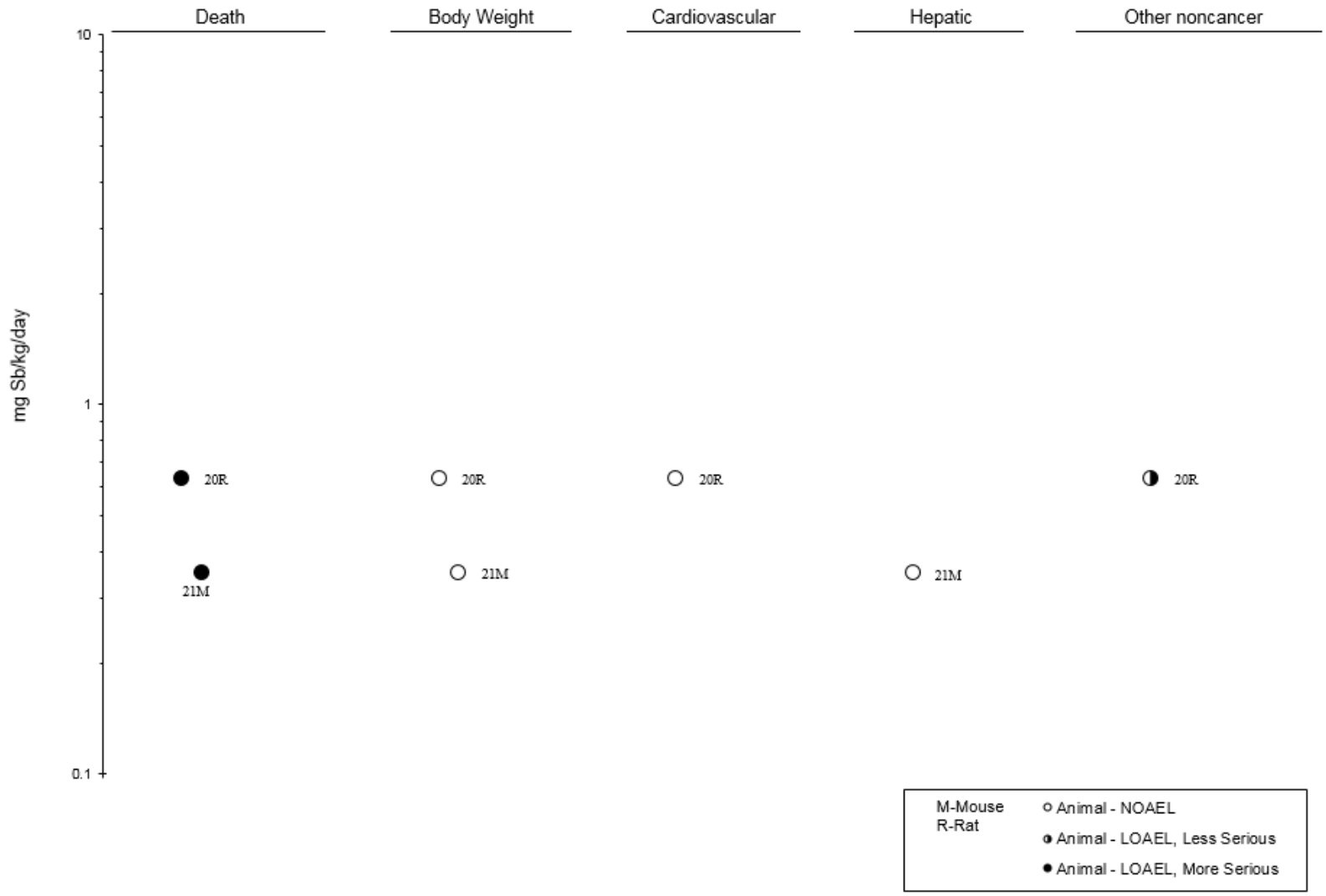


Table 2-5. Levels of Significant Exposure to Antimony – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Rat (Sprague-Dawley) 5 M, 5 F **Stibine** **NIOSH 1979**	30 minutes	0, 122, 799, 1,395 mg/m^3	CS, BW, GN	Ocular	122	799		Eye irritation and closure
Guinea pig (Hartley) 10 F **Antimony sulfide** **Horton et al. 1986**	4 times	0, 3.3, 6.6 mg	CS	Immuno	6.6			
Guinea pig (Hartley) 5 M, 5 F **Stibine** **NIOSH 1979**	30 minutes	0, 122, 799, 1,395 mg/m^3	CS, BW, GN, HP	Ocular	1,395			
Rabbit (NS) 10 M **Antimony trioxide** **Gross et al. 1955**	Once	84 mg	CS	Ocular	84			
Rabbit (NS) 8 NS **Antimony trioxide** **Gross et al. 1955**	Once	20,900 mg	CS	Dermal	20,900			
Rabbit (New Zealand) 12 NS **Antimony sulfide** **Horton et al. 1986**	Once	66 mg	CS	Ocular		66		Eye irritation
INTERMEDIATE EXPOSURE								
Rat (Fischer-344) 50 M, 50 F **Antimony trioxide** **Newton et al. 1994**	13 weeks, 6 hours/day, 5 days/week	0, 0.21, 0.902, 4.92, 19.60 mg/m^3	OP	Ocular		0.21		Corneal irregularities were observed (approximately 30% in each group)

Table 2-5. Levels of Significant Exposure to Antimony – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Rabbit (New Zealand) 10 M,10 F	13 weeks, 5 days/week	0, 6.5, 65 mg	CS, BW, HE, BC, OF, HP	Bd wt	65			
				Cardio	65			
				Hemato	65			
				Hepatic	65			
				Renal	65			
				Dermal	65			
				Endocr	65			
				Repro	65			
Antimony sulfide **Horton et al. 1986**								
CHRONIC EXPOSURE								
Rat (Wistar) 90 M, 90 F	52 weeks, 7 hours/day, 5 days/week	0, 36	CS	Dermal	36			
				Ocular	36			
Antimony trioxide **Groth et al. 1986**								
Rat (Wistar) 90 M, 90 F	52 weeks, 7 hours/day, 5 days/week	0, 17.5	CS	Dermal	17.5			
				Ocular	17.5			
ANTIMONY **Groth et al. 1986**								
Rat (Wistar) 50 M, 50 F	2 years, 6 hours/day, 5 days/week	0, 2.5, 8.3, 25	CS	Dermal	8.3 F	25 F		Chronic inflammation and ulcers of the skin
Antimony trioxide **NTP 2016**								

Table 2-5. Levels of Significant Exposure to Antimony – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mouse (B6C3F1) 50 M, 50 F	2 years, 6 hours/day, 5 days/week	0, 2.5, 8.3, 25	CS	Dermal	25			
				Ocular	25			
Antimony trioxide NTP 2016								

BC = serum (blood) chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; Repro = reproductive

2.2 DEATH

A study of NHANES participants reported an association between urinary antimony levels and increased risk of deaths from all causes (Guo et al. 2016); the results of this study are not adequate to establish a relationship between antimony and death.

Deaths occurred in guinea pigs exposed to approximately 37.9 mg Sb/m^3 as antimony trioxide dust for approximately 60–178 days (Dernehl et al. 1945) and in guinea pigs and rats exposed to 1,395 mg Sb/m^3 as stibine gas for 30 minutes (NIOSH 1979). Pulmonary edema was a contributing factor to the death of rats and guinea pigs exposed to stibine (NIOSH 1979). None of the rats or guinea pigs exposed to ≤799 mg Sb/m^3 for 30 minutes died (NIOSH 1979). Lower concentrations of antimony trisulfide (84–105 mg Sb/m^3), antimony trioxide (≥36 mg Sb/m^3), or antimony ore (17.5 mg Sb/m^3) did not affect the survival of rats exposed for approximately 1 year (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; Watt 1983). However, a 2-year exposure to ≥8.3 mg Sb/m^3 as antimony trioxide resulted in decreased survival in female rats and male and female mice (NTP 2016). The decreased survival was attributed to lung inflammation and/or lung carcinomas (mice only).

Mortality was not observed in rats following a single exposure to ≤188–17,000 mg Sb/kg as antimony trioxide (Fleming 1938; Myers et al. 1978; Smyth and Carpenter 1948; Smyth and Thompson 1945) or to a 7,000 mg Sb/kg dose of metallic antimony (Bradley and Frederick 1941). However, a lower single dose of organic antimony (300 mg Sb/kg dose as antimony potassium tartrate) resulted in death in rats (Bradley and Frederick 1941). Death was attributed to myocardial failure. Significant increases in deaths were not observed in rats or mice exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate in drinking water for 14 days (NTP 1992). These data for death in animals suggest that organic antimony is more lethal than the inorganic compounds, probably due to increased absorption of the antimony potassium tartrate, likely due to its increased solubility.

Intermediate-duration exposure to inorganic antimony compounds or metallic antimony did not result in increases in deaths in rats exposed to ≤1,570 mg Sb/kg/day as antimony trioxide in the diet (Hext et al. 1999; Hiraoka 1986) or ≤850 mg Sb/kg/day as metallic antimony (Hiraoka 1986). Chronic administration of a low dose of antimony potassium tartrate (0.63 mg Sb/kg/day) resulted in decreased lifespan in rats (Schroeder et al. 1970). A decrease in survival was also noted in female mice exposed to 0.35 mg Sb/kg/day as antimony potassium tartrate (Kanisawa and Schroeder 1969); however, there was no statistical analysis of the data.

In a repeated dermal exposure study, three of eight rabbits died due to exposure to antimony trioxide in an artificial sweat paste for 5–8 treatments; the remaining animals received 21 treatments and survived (Fleming 1938). Since the application area was not occluded, it is likely that the animals ingested the paste; the results of this study was therefore not included in the LSE table. Damage to the cardiac portion of the stomach was noted in two of the three rabbits that died. No antimony-related deaths were reported in rabbits exposed to 65 mg antimony as antimony sulfide in calcium cup grease for 13 weeks (Horton et al. 1986).

2.3 BODY WEIGHT

Data on possible associations between antimony and body weight in humans is limited to a study in children that examined body weight at 18 months of age and hair antimony levels at 20–36 months of age (Vigeh et al. 2017). No significant differences in hair antimony levels were found in children with body weights below the 50th percentile compared to those with body weights above the 50th percentile.

No alterations in body weight gain have been observed in inhalation studies in rats and mice exposed to antimony trioxide for acute (NTP 2016), intermediate (Belyaeva 1967; Newton et al. 1994), or chronic (Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983) durations at concentrations as high as 50, 209, or 36 mg Sb/m^3, respectively. No body weight alterations were observed in rats exposed to 17.5 mg Sb/m^3 as antimony ore for approximately 1 year (Groth et al. 1986).

Similarly, most oral exposure studies have not reported decreases in body weight gain in laboratory animals exposed to metallic antimony, antimony trioxide, or antimony potassium tartrate (Angrisani et al. 1988; Fleming 1938; Hext et al. 1999; Hiraoka 1986; Kanisawa and Schroeder 1969; NTP 1992; Poon et al. 1998; Schroeder et al. 1970; Sunagawa 1981). Four studies did report decreases in body weight and/or weight loss. NTP (1992) reported significant decreases in body weight gain in mice exposed to 99 mg Sb/kg/day (males) or 150 mg Sb/kg/day (males and females). Although these decreases in body weight gain were observed midway through the 2-week study, the body weights of all groups of mice were within 93% of the controls at termination. Decreases in body weight gain (body weights were 11–18% lower than controls) were observed in rats exposed to ≥85 mg Sb/kg/day as metallic antimony for 12 weeks; the lower body weights in the 850 mg Sb/kg/day group were still lower than controls after a 12-week recovery period (Hiraoka 1986). Smyth and Thompson (1945) reported a decrease in body weight gain in rats exposed to 890 mg Sb/kg/day as antimony trioxide in the diet for 30 days; however, a

decrease in food intake was also observed at that dose level. A fourth study reported an 11% decrease in maternal weight gain in rats exposed to 0.7 mg Sb/kg/day as antimony trichloride in drinking water during gestation and lactation (Rossi et al. 1987).

No dermal exposure studies examining body weight were identified.

2.4 RESPIRATORY

Studies of workers exposed to antimony compounds (primarily antimony trioxide) have reported upper and lower respiratory effects. Upper respiratory effects included soreness and bleeding of the nose, rhinitis, and laryngitis in workers at an antimony smelter (Renes 1953). One of the more commonly reported lower respiratory effects is pneumoconiosis in workers involved in extraction of antimony trioxide from antimony ores and workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Other lower respiratory effects include chronic coughing, upper airway inflammation, and chronic bronchitis (Potkonjak and Pavlovich 1983). In the two studies that conducted lung function tests, no consistent pattern of alterations was found (Cooper et al. 1968; Potkonjak and Pavlovich 1983). Three studies provided some monitoring data. In the study reporting upper respiratory effects, the average antimony concentrations were 10.07–11.81 mg/m^3 (Renes 1953). In the two studies reporting pneumoconiosis, antimony levels were 0.081–138 mg/m^3 in one study (Cooper et al. 1968) and 0.747 mg/m^3 (geometric mean concentration) in the second study (Schnorr et al. 1995). Several studies reported that the workers were also exposed to arsenic, which was present in the antimony ores (Jones 1994; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995); the workers were also exposed to other compounds including iron oxide and hydrogen sulfide (Potkonjak and Pavlovich 1983; Renes 1953). In contrast to these studies of workers exposed to antimony ores and/or antimony oxides, respiratory irritation was not noted in workers exposed to ≤3.9 mg Sb/m^3 as antimony trisulfide for 8 months to 2 years (Brieger et al. 1954).

Studies in laboratory animals, particularly rats, support the findings of the epidemiology studies and suggest that the respiratory tract is one of the most sensitive targets of inhaled antimony toxicity. The lungs appear to be the most sensitive portion of the respiratory tract, and the severity of the respiratory effects appear to be concentration- and duration-related. Although most of the studies were conducted using antimony trioxide, studies with stibine (NIOSH 1979), antimony trisulfide (Brieger et al. 1954), and antimony ore (Groth et al. 1986) have also reported lung effects.

Exposure to antimony aerosols results in deposition of the particles in the lungs, which leads to increases in the number of alveolar macrophages, inflammation, and fibrosis. The earliest and most sensitive effect of inhaled antimony is increased alveolar and/or intra-alveolar macrophages. Intermediate- and chronic-duration studies found increases in alveolar and/or intra-alveolar macrophages in rats exposed to concentrations as low as 4.11 mg Sb/m^3 as antimony trioxide following a 13-week exposure (Newton et al. 1994) and 0.05 mg Sb/m^3 as antimony trioxide following a 1-year exposure (Newton et al. 1994). The increases in macrophages persisted for at least 27 weeks or 1 year, respectively, after exposure termination. The proliferation of macrophages is a normal physiological response to the deposition of insoluble particulates in the lung and increases in the number of alveolar macrophages in the absence of evidence of lung damage were not considered adverse. The increases in antimony lung deposition also resulted in increases in lung clearance half-times. Following a 13-week exposure (Newton et al. 1994), the lung clearance half-times were 5.5 and 5.25 months in male and female rats, respectively, exposed to 4.11 mg Sb/m^3 and 10 and 8.25 months in male and female rats, respectively, exposed to 19.60 mg Sb/m^3; by comparison, the half-times were 3.75 months in both male and female rats exposed to 0.902 mg Sb/m^3. Similarly, in the 1-year exposure study (Newton et al. 1994; data reported in Bio/Dynamics 1990), the antimony lung clearance half-times in male and female rats were 3.0 and 4.2 months, respectively, at 0.43 mg Sb/m^3 and 8.7 and 10.2 months, respectively, at 3.8 mg Sb/m^3, as compared to 2.5 and 2.2 months, respectively, in the 0.05 mg Sb/m^3 group. The investigators noted that the decrease in lung clearance was higher than anticipated if it was solely due to volumetric overloading, suggesting that clearance was also affected by the intrinsic toxicity of antimony trioxide. In a 2-year study using smaller particles (mass median aerodynamic diameter [MMAD] of 1.0–1.4 μm compared to 3.05 μm in the Newton et al. [1994] study), estimated clearance half-times were 136, 206, and 262 days (approximately 4.5, 6.8, and 8.6 months) for exposures to 2.5, 8.3, and 25 mg Sb/m^3, respectively, as antimony trioxide (NTP 2016).

The lowest antimony trioxide concentrations resulting in histological alterations (lung inflammation) in rats are 19.60 and 0.43 mg Sb/m^3 in intermediate- and chronic-duration studies (Newton et al. 1994), respectively. In both studies, the increases in the incidence of lung inflammation were observed at the end of a 27-week or 1-year recovery period; these effects were not observed at the end of the exposure period (highest concentrations tested were 19.60 and 3.8 mg Sb/m^3 in the intermediate and chronic studies, respectively). In contrast, NTP (2016) found significant increases in the incidence in chronic inflammation and other lung lesions in rats exposed to ≥2.5 mg Sb/m^3 for 1 year; the smaller particle size in the NTP (2016) study may explain the difference between the studies. The lowest concentrations in mice resulting in lung inflammation are 25 mg Sb/m^3 following a 16-day exposure and 0.25 mg Sb/m^3

following a 2-year exposure (NTP 2016). Inflammation was also observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954) and in guinea pigs after intermediate-duration exposure to 37.9 mg Sb/m^3 as antimony trioxide (Dernehl et al. 1945). Chronic exposure to higher concentrations (≥1.6 mg Sb/m^3 as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore) resulted in lung fibrosis in rats (Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983). Other lesions observed in the lungs include proteinosis and alveolar/bronchiolar epithelial hyperplasia in rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 1 or 2 years (NTP 2016), pulmonary edema and congestion in rats and guinea pigs exposed to a lethal stibine concentration of 1,395 mg Sb/m^3 for 30 minutes (NIOSH 1979), alveolar hypertrophy and hyperplasia and cholesterol clefts in rats exposed to 36 mg Sb/m^3 as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore for 52 weeks (Groth et al. 1986) or rats exposed to 4.2 mg Sb/m^3 for 55 weeks (Watt 1983), lipoid pneumonia in rats exposed to 84–105 mg Sb/m^3 as antimony trioxide for 14.5 months (Gross et al. 1952), and focal hemorrhages in the lungs of rats exposed to 2.20 mg Sb/m^3 as antimony trisulfide for 6 weeks (Brieger et al. 1954).

The NTP (2016) 2-year antimony trioxide study also reported hyperplasia of the nasal respiratory epithelium in rats exposed to ≥2.5 mg Sb/m^3, squamous metaplasia of the respiratory epithelium in rats and mice exposed to 25 mg Sb/m^3, laryngeal epithelial hyperplasia in mice exposed to ≥8.3 mg Sb/m^3, and hyperplasia of tracheal epithelium in mice exposed to 25 mg Sb/m^3.

Oral exposure studies have not reported respiratory tract lesions in humans or laboratory animals. In the only human study examining respiratory endpoints, no significant association between urinary antimony levels and the prevalence of asthma was found among participants in the 2007–2008 NHANES (Mendy et al. 2012).

No histological alterations were observed in the respiratory tract in several oral exposure studies at the highest doses tested; the highest NOAEL values were 61 or 150 mg Sb/kg/day in rats or mice, respectively, exposed to antimony potassium tartrate in drinking water for 14 days (NTP 1992), 1,408 mg Sb/kg/day in rats exposed to antimony trioxide in the diet for 90 days (Hext et al. 1999), and 42.17 mg Sb/kg/day in rats exposed to antimony potassium tartrate in drinking water for 13 weeks (Poon et al. 1998).

No studies were located regarding respiratory effects in humans following dermal exposure to antimony. Hyperemia in the lungs was observed in a rabbit that died after six or eight applications of an antimony trioxide paste to shaven and abraded skin. The antimony trioxide (concentration not reported) was

combined with a mixture resembling acidic sweat (Fleming 1938). The application area was not occluded; thus, the ingestion of the paste likely occurred and the results of this study was not included in the LSE table.

2.5 CARDIOVASCULAR

Altered EKG readings were observed in workers exposed to 0.42–3.9 mg Sb/m^3 as antimony trisulfide for 8 months to 2 years (Brieger et al. 1954). Of the 75 workers examined, 37 showed changes in the EKG, mostly of the T-waves; these workers had also been exposed to phenol formaldehyde resin (Brieger et al. 1954). In a cohort mortality study, an increase in death from ischemic heart disease was observed among antimony smelter workers with Spanish surnames (Schnorr et al. 1995); the statistical significance of this finding was not reported. Guo et al. (2016) did not find an association between urinary antimony levels in NHANES participants and deaths from heart disease. However, the study did find association for the risks of self-reported heart disease, congestive heart failure, and heart attack; no associations were found for self-reported angina pectoris or coronary heart disease. Another study of NHANES participants did not find an association between urinary antimony levels and peripheral arterial disease (Navas-Acien et al. 2005).

These limited data on cardiovascular effects in humans are supported by the finding of cardiac effects following parenteral administration of antimony to humans. Alterations in EKGs, particularly prolongation of QT interval, have been reported following injection of sodium antimony tartrate (Honey 1960), sodium antimony gluconate (Dancaster et al. 1966; Lawn et al. 2006; Sundar et al. 1998; Thakur 1998), sodium stibogluconate (Pandey et al. 1988), and meglumine antimoniate (Neves et al. 2009). Whereas a very high incidence was reported in patients treated with sodium antimony tartrate (98%, with 30% categorized as severe EKG changes) (Honey 1960), a much lower incidence (8–25%) was found in patients treated with pentavalent antimony (Dancaster et al. 1966; Neves et al. 2009). The cardiotoxicity of antimony (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966) and the differences in the cardiotoxicity of trivalent and pentavalent antimony (Alvarez et al. 2005) are supported by animal studies. Whereas intramuscular injections of 16 mg Sb/kg/day as meglumine antimoniate for 26 days resulted in a slight prolongation of the QT duration in guinea pigs, intramuscular administration of 10 mg Sb/kg/day as antimony potassium tartrate for 8–12 days resulted in bradycardia and a more marked elongation of the QT interval (Alvarez et al. 2005).

Inhalation exposure to antimony trisulfide dust (dust sample taken from an antimony production facility) resulted in degenerative changes in the myocardium and related EKG abnormalities (elevation of the RS-T segments and flattening of T-waves) in a variety of animal species (Brieger et al. 1954). Five days of exposure to 19.9 mg Sb/m^3 as antimony trisulfide resulted in EKG alterations in rabbits. In intermediate-duration studies, EKG alterations were observed in rats, rabbits, and dogs exposed to 2–4 mg Sb/m^3 as antimony trisulfide for 6–10 weeks (Brieger et al. 1954). It should be noted that elevated levels of arsenic were also present in the facilities' dust samples. This study also reported degenerative changes of the myocardium in rats, rabbits, and dogs exposed to antimony trisulfide, which consisted of hyperemia and swelling of myocardial fibers (Brieger et al. 1954). Most studies with antimony trioxide exposure did not find cardiovascular effects. No EKG alterations were observed in pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide for 1 year (Watt 1983) or guinea pigs exposed to 37.9 mg Sb/m^3 for an intermediate-duration (Dernehl et al. 1945), and myocardial damage was not observed in rats exposed to concentrations as high as 19.60 mg Sb/m^3 for 13 weeks (Newton et al. 1994) or 36 mg Sb/m^3 for approximately 1 year (Groth et al. 1986; Newton et al. 1994; Watt 1980) or guinea pigs exposed to 37.9 mg Sb/m^3 for 2–30 weeks (Dernehl et al. 1945). NTP (2016) found chronic inflammation of the epicardium of mice exposed to ≥8.3 mg Sb/m^3 for 2 years and chronic inflammation of muscular arteries in rats exposed to ≥8.3 mg Sb/m^3.

Several investigators have utilized the NHANES dataset to examine the possible association between antimony and cardiovascular toxicity. No significant associations were found between urinary antimony levels and the prevalence of congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke (Mendy et al. 2012). In two studies, significant associations between urinary antimony levels and the prevalence of high blood pressure were found in adults (Shiue and Hristova 2014; Shiue 2014); antimony accounted for 6.2% of the population risk (Shiue and Hristova 2014).

No histopathological alterations were observed in the heart following acute-duration oral exposure of rats and mice to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992) or following intermediate-duration exposure to 1,408 mg Sb/kg/day as antimony trioxide (Hext et al. 1999) or 42.17 mg Sb/kg/day as antimony potassium tartrate (Poon et al. 1998). In studies evaluating cardiovascular function, no significant alterations in blood pressure were observed in rats exposed to 0.7 mg Sb/kg/day as antimony trichloride during pregnancy and/or lactation (Angrisani et al. 1988; Marmo et al. 1987; Rossi et al. 1987) or rats chronically exposed to 0.63 mg Sb/kg/day as antimony potassium tartrate (Schroeder et al. 1970). Alterations in vasomotor responses were observed in pups exposed to antimony chloride; these effects are discussed under Developmental Effects.

No studies were located regarding cardiovascular effects in humans following dermal exposure to antimony. Application of 65 mg antimony as antimony sulfide in calcium cup grease did not result in alterations in EKG readings or heart pathology in rabbits (Horton et al. 1986).

Several *in vitro* studies have investigated the cardiotoxicity of antimony, particularly damage to the myocytes, which results in cell death and alterations and could lead to abnormalities in EKGs and arrhythmias. Tirmenstein (1995, 1997) found that exposure to antimony potassium tartrate resulted in several biochemical alterations in cardiac myocytes including the disruption of cellular thiol homeostasis, particularly the depletion of glutathione, induction of lipid peroxidation, and binding to vicinal thiols such as pyruvate dehydrogenase. The inhibition of pyruvate dehydrogenase subsequently leads to a decrease in cellular ATP levels. These biochemical alterations all contribute to cell death. Additionally, exposure to antimony potassium tartrate disrupts calcium homeostasis in myocytes. Wey et al. (1997) found a progressive elevation of resting (or diastolic) transient calcium levels in myocytes and an eventual cessation of beating activity that preceded cell death. Further investigations by this group found that antimony potassium tartrate reduced calcium availability during excitation-contraction and that there was a decreased flux of calcium through voltage-dependent L-type calcium channels in the myocyte (Toraason et al. 1997). The decreased influx of calcium was likely due to enhanced removal of calcium (Toraason et al. 1997). The investigators noted that the reduced influx and enhanced efflux of calcium could account for the reduced cardiac output observed in *in vivo* studies. Another study found that trivalent antimony increased cardiac calcium currents, resulting in a prolonged action potential (Kuryshev et al. 2006). The prolonged action potential results in a delay in cardiac repolarization, which could explain the QT prolongation observed in EKGs and arrhythmias in humans administered antimony for the treatment of leishmaniasis (Kuryshev et al. 2006). Similar findings were observed in myocytes exposed to pentavalent antimony, although the investigators concluded that this was likely due to the conversion of pentavalent antimony to trivalent antimony. Pentavalent antimony also increased sodium current amplitude, which was not observed in trivalent antimony exposed myocytes. However, the change in sodium current amplitude was not likely to contribute to arrhythmia since it was not accompanied by any obvious changes in channel gating (Kuryshev et al. 2006).

2.6 GASTROINTESTINAL

A variety of gastrointestinal symptoms have been reported in workers with acute exposure to antimony trichloride (Taylor 1966) and chronic exposure to antimony trisulfide (Brieger et al. 1954) or antimony

oxide (Renes 1953). The symptoms include abdominal pain, diarrhea, vomiting, and ulcers. A causal relationship to antimony exposure has not been definitely established because workers were exposed to a variety of other agents, in addition to antimony, that might cause or contribute to gastrointestinal effects (e.g., hydrogen chloride, sodium hydroxide), and the studies did not examine unexposed workers. Furthermore, in all likelihood, both inhalation and oral exposure to antimony occur at the workplace. Assuming that gastrointestinal effects are related to antimony exposure, site monitoring data indicate that effective exposure levels may range from approximately 2 to 70 mg Sb/m^3.

Symptoms of gastrointestinal disturbances were not reported in animals exposed to airborne antimony compounds, and no histopathological alterations were observed in rats exposed to ≤36 mg Sb/m^3as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore for 1 year (Groth et al. 1986; Watt 1980) or pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide for 55 weeks (Watt 1983). However, chronic active inflammation was observed in the forestomach of mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016).

Shortly after drinking lemonade contaminated with antimony potassium tartrate, workers began to vomit (Dunn 1928). Vomiting was observed in dogs following a single exposure to antimony potassium tartrate (Houpt et al. 1984). Other studies have not reported overt signs of gastrointestinal effects in rats or mice following acute- or intermediate-duration exposures to antimony trioxide or antimony potassium tartrate (Fleming 1938; Hext et al. 1999; NTP 1992; Poon et al. 1998). Focal ulceration was observed in the forestomach of mice exposed to 150 mg Sb/kg/day as antimony potassium tartrate for 2 weeks (NTP 1992). Histological alterations were not observed in rats (Hext et al. 1999; NTP 1992; Poon et al. 1998).

No studies were located regarding gastrointestinal effects in humans following dermal exposure to antimony. Hemorrhages in the cardiac portion of the stomach were observed in a rabbit that died after six or eight applications of an antimony trioxide-acidic sweat paste (Fleming 1938). Because the application area was not occluded, ingestion of the paste is possible; the results of this study was therefore not included in the LSE table.

2.7 HEMATOLOGICAL

Information on the hematological toxicity of inhaled antimony is limited to a case report of three workers exposed to stibine, arsine, and hydrogen sulfide (Dernehl et al. 1944). Two of the three workers reported hematuria with weakness, headache, and abdominal and lumbar pain. It is not known if stibine was the

causative agent of these effects. No studies were located regarding hematological effects in humans after inhalation exposure to other antimony compounds.

Toxicologically significant hematological effects have not been observed in rats and pigs following intermediate- or chronic-duration inhalation exposure to antimony aerosols ranging from approximately 4 to 20 mg Sb/m^3 as antimony trioxide (Newton et al. 1994; Watt 1983). One study reported decreases in total leukocyte counts and in polymorphonuclear leukocyte and eosinophil counts in guinea pigs exposed to 36.9 mg Sb/m^3 as antimony trioxide for 2–30 weeks (Dernehl et al. 1945) and another study reported hematopoietic cell proliferation in the spleen of female mice exposed to 25 mg Sb/m^3 for 2 years (NTP 2016).

No studies were located regarding hematological effects in humans after oral exposure to antimony. Animal studies have examined potential hematological effects of three antimony compounds (metallic antimony, antimony trioxide, and antimony potassium tartrate) following intermediate-duration exposure. No alterations in hemoglobin levels or hematocrit were observed in rats exposed to 850 mg Sb/kg/day as metallic antimony; however, a decrease in hematocrit level was observed 4 weeks postexposure (Hiraoka 1986). In a second study, no consistent dose-related alterations in red blood cell counts were observed in rats exposed to 370–1,500 mg Sb/kg/day; however, significant decreases in hemoglobin and hematocrit were observed at 1,500 mg Sb/kg/day (Sunagawa 1981). Mixed results were found for antimony trioxide. Smyth and Thompson (1945) reported an increase in red blood cell count in rats at 894 mg Sb/kg/day and Sunagawa (1981) reported a decrease in red blood cell counts at 620 mg Sb/kg/day; neither study found alterations in hemoglobin levels. In contrast, no alterations in hematological parameters (including red blood cell counts) were found in rats exposed to 700 mg Sb/kg/day (Hiraoka 1986) or 1,408 mg Sb/kg/day (Hext et al. 1999). Decreases in red blood cell and platelet counts were observed in male rats exposed to 42.17 mg Sb/kg/day as antimony potassium tartrate; no effects were found in female rats (Poon et al. 1998). The inconsistent findings across studies and compounds preclude determining whether antimony adversely affects the hematological system.

No studies were located regarding hematological effects in humans following dermal exposure to antimony. No alterations in hematological indices were observed in rabbits exposed to 65 mg antimony as antimony sulfide for 13 weeks (Horton et al. 1986).

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans after inhalation exposure to antimony. No histopathological alterations were noted in the musculoskeletal system in rats exposed to 4.2 mg Sb/m^3 as antimony trioxide for 1 year (Watt 1980). Bone marrow hyperplasia was observed in rats exposed to 25 mg Sb/m^3 and mice exposed to ≥2.5 mg Sb/m^3 for 2 years (NTP 2016); the investigators noted that the hyperplasia in the mice was predominantly of myeloid cell type, which may have been secondary to the lung inflammation.

Shiue (2015) found a significant association between urinary antimony levels and one of the three clinical measures of ankylosing spondylitis among adults participating in the NHANES; however, no associations were found for the other two measures of ankylosing spondylitis. No histological alterations in musculoskeletal tissue were observed in rats or mice acutely exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992) or in rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999).

2.9 HEPATIC

No studies were located regarding hepatic effects in humans after inhalation exposure to antimony. Parenchymatous or fatty degeneration was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954) and in guinea pigs exposed to 37.9 mg Sb/m^3 as antimony trioxide for 2–30 weeks (Dernehl et al. 1945). No hepatic effects were observed in rats exposed to ≤36 mg Sb/m^3 as antimony trioxide for 1 year (Groth et al. 1986; Watt 1983) or 17.5 mg Sb/m^3 as antimony ore (Groth et al. 1986), or in rats or mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016).

Mendy et al. (2012) did not find a significant association between urinary antimony levels and liver conditions among NHANES participants. Minimal to mild hepatocellular cytoplasmic vacuolization, primarily in the centrilobular region, was observed in mice exposed to 150 mg Sb/kg/day as antimony potassium tartrate for 2 weeks (NTP 1992). Minimal cloudy swelling of the hepatic cords has been observed in rats exposed to 620 mg Sb/kg/day as antimony trioxide or 740 mg Sb/kg/day as metallic antimony for 24 weeks (Sunagawa 1981). Increases in the incidence of nuclear anisokaryosis and hepatocellular portal density were observed in all groups of rats exposed to antimony potassium tartrate in the drinking water for 13 weeks (Poon et al. 1998); the severity of either alteration was considered mild in

males at ≥5.58 mg Sb/kg/day and in females at ≥0.64 mg Sb/kg/day. However, these alterations are adaptative changes and were not considered to be biologically adverse. Other studies have not found hepatic effects at doses as high as 61 mg Sb/kg/day as antimony potassium tartrate in rats for 14 days (NTP 1992), 1,408 mg Sb/kg/day as antimony trioxide in rats for 90 days (Hext et al. 1999), or 0.35 mg Sb/kg/day as antimony potassium tartrate in mice for lifetime exposure (Kanisawa and Schroeder 1969).

Two studies reported alterations in serum cholesterol levels in rats exposed to antimony potassium tartrate; however, one study reported a decrease in female rats exposed to 45.69 mg Sb/kg/day (Poon et al. 1998), and the other reported an increase in rats exposed to 0.63 mg Sg/kg/day (Schroeder et al. 1970).

No studies were located regarding hepatic effects in humans following dermal exposure to antimony. No alterations in serum clinical chemistry parameters or histopathology of the liver were observed in rabbits exposed to 65 mg antimony as antimony sulfide for 13 weeks (Horton et al. 1986).

2.10 RENAL

No studies were located regarding renal effects in humans after inhalation, oral, or dermal exposure to antimony. A small number of laboratory animal studies have reported renal effects following inhalation or dermal exposure to antimony. In acute-duration inhalation studies, tubular dilation was observed in guinea pigs exposed to 799 mg Sb/m^3 as stibine gas for 30 minutes (NIOSH 1979) and parenchymatous degeneration was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954). A 2-year inhalation exposure antimony trioxide study reported an increase in hyaline droplet accumulation at ≥8.3 mg Sb/m^3 in female rats and 25 mg Sb/m^3 in males and nephropathy at 25 mg Sb/m^3 in female rats (NTP 2016). Increases in blood urea nitrogen and creatinine levels were observed in male rabbits dermally exposed to 65 mg antimony as antimony sulfide; however, the levels were within the normal species variation and no histological alterations were observed in the kidneys (Horton et al. 1986). Other chronic inhalation studies and oral studies have not reported renal effects. No renal histological alterations were noted in rats exposed via inhalation to 17.5 mg Sb/m^3 as antimony ore or up to 36 mg Sb/m^3 as antimony trioxide for 1 year (Groth et al. 1986; Watt 1983) or in mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016). Similarly, no histological alterations were observed in the kidneys of rats and mice acutely exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992), rats exposed to ≤1,408 mg Sb/kg/day as antimony trioxide for an intermediate duration (Hext et al. 1999; Smyth and Thompson 1945), or rats exposed to 42.17 mg Sb/kg/day as antimony potassium tartrate for an intermediate duration (Poon et al. 1998).

2.11 DERMAL

Dermal effects have been reported in workers exposed to antimony oxides. These effects are likely due to direct skin contact with the antimony. Several studies have reported dermatitis in workers exposed to airborne antimony dust (Potkonjak and Pavlovich 1983). The dermatitis associated with exposure to airborne antimony is characterized as epidermal cellular necrosis with associated acute inflammatory cellular reactions (Stevenson 1965). The dermatitis is seen more often during the summer months and in workers exposed to high temperatures (Potkonjak and Pavlovich 1983; Stevenson 1965). Stevenson (1965) concluded that the dermatitis resulted from the action of antimony trioxide on the dermis after dissolving in sweat and penetrating the sweat glands. Transferring the worker to a cooler environment often resulted in the rash clearing up within 3–14 days. Antimony trioxide is not a skin sensitizer in humans following topical application (see Section 2.14).

In general, animal studies involving exposure to airborne antimony have not reported dermal effects (Groth et al. 1986; Newton et al. 1994). In a 13-week rat study (Newton et al. 1994 as reported in Bio/Dynamics 1985), alopecia was observed in females exposed to 0.902 or 4.11 mg Sb/m^3, but not females exposed to 19.60 mg Sb/m^3 or in males. Additionally, alopecia was not observed in a 1-year study conducted by this group (Newton et al. 1994). No dermal effects were observed in rats exposed to antimony trioxide in drinking water for 13 weeks at doses as high as 42.17 mg Sb/kg/day (Poon et al. 1998).

No evidence of skin irritation were observed in rabbits dermally exposed to 20,900 mg antimony as antimony trioxide (Gross et al. 1955). An intermediate-duration dermal exposure study did not report antimony-related skin irritation in rabbits exposed to 65 mg antimony as antimony sulfide (Horton et al. 1986); hyperkeratosis was observed in the vehicle control and antimony groups at similar incidences.

2.12 OCULAR

Eye irritation and damage has been observed in humans and animals exposed to airborne antimony or following instillation into the eye. Eye irritation was reported in 27.5% of workers at an antimony smelter; it is unclear if this was due to antimony oxides or other constituents in the smelter dust (Potkonjak and Pavlovich 1983). Eye irritation and closure were observed in rats exposed to ≥799 mg Sb/m^3 as stibine gas (NIOSH 1979); eye irritation was not noted in similarly exposed guinea pigs (NIOSH

1979). Exposure to airborne antimony trioxide resulted in corneal opacities in rats exposed to ≥0.21 mg Sb/m^3 for 13 weeks (Newton et al. 1994), and cataracts (focal posterior cataracts, posterior subcapsular cataracts, and complete cataracts) were observed in rats exposed to ≥0.43 mg Sb/m^3 for 1 year followed by a 1-year recovery period (Newton et al. 1994). An increase in the incidence of chromodacryorrhea was also observed in the chronic study; the investigators suggested that this may have been secondary to dental abnormality, infectious disease, or xerosis. NTP (2016) reported an increased incidence of ciliary body inflammation in rats exposed to 25 mg Sb/m^3 for 2 years. A non-concentration-related increase in retinal atrophy was also observed in female rats exposed to ≥2.5 mg Sb/m^3 (NTP 2016); the severity of the atrophy was similar to that observed in the concurrent controls. It is not known if these effects are due to direct contact or are systemic effects. Instillation of 66 mg antimony as antimony sulfide into the eyes of rabbits resulted in eye irritation (Horton et al. 1986).

No histological alterations were observed in the eyes of rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999).

No evidence of eye irritation was observed in rabbits following instillation of 84 mg antimony as antimony trioxide (Gross et al. 1955). In contrast, conjunctival erythema, chemosis, and ocular discharge were observed 24 hours after instillation of 66 mg antimony as antimony sulfide (Horton et al. 1986). Seven day post-exposure, superficial corneal injury was observed in a third of the rabbits.

2.13 ENDOCRINE

Histological alterations have not been observed in the thyroid glands of laboratory animals following chronic exposure to concentrations as high as 36 mg Sb/m^3 as antimony trioxide (Groth et al. 1986; NTP 2016; Watt 1983) or 17.5 mg Sb/m^3 as antimony ore (Groth et al. 1986).

No significant association between urinary antimony levels and self-reported thyroid conditions were found in NHANES participants (Mendy et al. 2012). In general, oral studies examining endocrine organs have not reported adverse effects at 61 or 150 mg Sb/kg/day as antimony potassium tartrate in rats and mice exposed for 14 days (NTP 1992) or in rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999). Poon et al. (1998) reported minimal to mild epithelial changes in the thyroid of rats exposed to ≥0.06 mg Sb/kg/day; however, the alterations were not dose-related and did not appear to affect thyroid function, and the investigators did not consider them adverse.

2.14 IMMUNOLOGICAL

Two studies examined the possible immunotoxicity of antimony in workers. Both studies evaluated serum immunoglobin levels. Kim et al. (1999) reported decreases in IgG2 and IgE levels in antimony trioxide workers. Wu and Chen (2017) also reported decreases in serum IgG, IgA, and IgE levels among antimony trioxide and sodium antimonite workers. This study also found significant inverse correlations between air antimony levels and IgG, IgA, and IgE levels and between blood, urine, and hair antimony levels and IgA and IgE levels.

No animal studies evaluated immune function following inhalation exposure to antimony. In chronic-exposure studies, hyperplasia of the reticuloendothelial cells in the peribronchiolar lymph nodes was observed in female rats exposed to 3.8 mg Sb/m^3 as antimony trioxide for 1 year with a 1-year recovery period (Newton et al. 1994), and lymphoid hyperplasia was observed in the bronchial and mediastinal lymph nodes of rats and mice exposed to ≥2.5 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016). Another study reported the presence of mononuclear cell granulomas in rats exposed to17.5 mg Sb/m^3 as antimony ore for 1 year (Groth et al. 1986); this effect was not found in rats similarly exposed to 36 mg Sb/m^3 as antimony trioxide (Groth et al. 1986). The investigators noted that the granulomas were similar to those found in the early stages of silicosis and sarcoidosis.

No studies were located regarding immunological effects in humans after oral exposure to antimony. Limited information on the immunotoxicity of antimony is available in animals. In the thymus of rats exposed to antimony potassium tartrate for 13 weeks, increases in medullary volume were observed in males exposed to ≥0.56 mg Sb/kg/day and in females exposed to ≥6.13 mg Sb/kg/day; a decrease in cortical volume was also observed in females exposed to ≥6.13 mg Sb/kg/day (Poon et al. 1998). The biological significance of these findings is not known.

No studies were located regarding immunological effects in humans following dermal exposure to antimony. In a skin sensitization assay, 6.6 mg antimony as antimony sulfide in liquid petrolatum did not result in sensitization in guinea pigs (Horton et al. 1986). When the antimony sulfide was administered in calcium cup grease, a positive result for sensitization was found; however, this was likely due to the vehicle, since no reaction was found when antimony sulfide in petrolatum was used as the challenge agent (Horton et al. 1986).

2.15 NEUROLOGICAL

A causal relationship between exposure to airborne antimony and neurological effects in humans has not been established. Nerve tenderness and a tingling sensation, headaches, and prostration were reported in workers exposed to antimony oxide at a concentration of 10.07 mg Sb/m^3 (Renes 1953). However, the factory workers were also exposed to arsenic, lead, copper, and possibly hydrogen sulfide and sodium hydroxide. Thus, it is difficult to determine if this effect was the result of antimony exposure. Another study attempted to link air monitoring levels of antimony with the risk of Parkinson's disease in nurses and did not find a significant association (Palacios et al. 2014); it should be noted that the air concentrations were very low (the median level in the highest quartile was 0.000682 μg/m^3). In a study utilizing the NHANES database, Scinicariello et al. (2017) found associations between urinary antimony levels and several self-reported sleep-related disorders including insufficient sleep duration (≤6 hours/night), prolonged sleep-onset latency (>30 minutes per night), obstructive sleep apnea, sleep problems, and day-time sleepiness.

Several studies have evaluated the possible relationship between urinary or hair antimony and autism or autism spectrum disorder. Studies of children have not found significant differences between hair antimony or urine antimony levels in children with autism or autism spectrum disorder compared to controls (Adams et al. 2006; Blaurock-Busch et al. 2011; Fido and Al-Saad 2005). A fourth study found no association between urinary antimony levels and autism severity (Adams et al. 2013). A meta-analysis of four studies (Adams et al. 2006; Blaurock-Busch et al. 2011; Fido and Al-Saad 2005; Saghazadeh and Rezaei 2017) found slightly higher hair antimony levels among children with autistic spectrum disorder than in controls (standardized mean difference 0.24, 95% confidence interval [CI] 0.03–0.45) (Saghazadeh and Rezaei 2017). It is noted that the observational studies and the meta-analysis did not account for potential confounding factors and was based a small number of subjects (181 cases and 185 controls in the meta-analysis).

None of the available laboratory animal studies adequately examined the potential neurotoxicity of antimony following inhalation, oral, or dermal exposure. No histological alterations were observed in the brains following acute- and intermediate-duration oral exposure (Hext et al. 1999; NTP 1992; Poon et al. 1998) or chronic-duration inhalation exposure to antimony trioxide (Groth et al. 1986; NTP 2016; Watt 1983).

2.16 REPRODUCTIVE

Disturbances in the menstrual cycle were reported in 61.2% of women exposed to airborne metallic antimony, antimony pentasulfide, and antimony trioxide in a metallurgical plant compared to the 35.7% occurrence in controls (Belyaeva 1967); no other details were provided. No information (such as age and whether they had similar jobs as the workers) was provided that could be used to evaluate the appropriateness of the control group. The investigators noted that 77.5% of the workers and 56% of the controls had reproductive disturbances. The study also found an increase in the rate of spontaneous abortions (particularly late term abortions) in the workers (12.5%) as compared to the rate in controls (4.1%). In a study of men of subfertile couples, no associations between urinary antimony levels and reproductive hormone levels (estradiol, follicle stimulating hormone, testosterone, or sex hormone-binding hormone) were reported (Wang et al. 2016).

Data on the reproductive toxicity of inhaled antimony are limited to an intermediate-duration study conducted by Belyaeva (1967), which found a reduction in fertility (67% conceived compared to 100% in controls) in rats exposed to 209 mg Sb/m^3 as antimony trioxide. No histological alterations were observed in the reproductive tissues of rats exposed to antimony trioxide or antimony ore for 1 year (Groth et al. 1986; Watt 1983) or mice exposed to antimony trioxide for 2 years (NTP 2016). Increases in the incidence of epithelial hyperplasia were observed in the prostate of rats exposed to 2.5 or 8.3 mg Sb/m^3 for 2 years (NTP 2016).

No studies were located regarding reproductive effects in humans after oral exposure to antimony. Information on the reproductive toxicity of antimony in laboratory animals is limited to a series of experiments conducted by Omura et al. (2002). No significant alterations in sperm count, motility, or morphology or histological alterations of the testes were observed in rats and mice exposed to 1,000 mg Sb/kg/day as antimony trioxide or 10 mg Sb/kg/day as antimony potassium tartrate.

2.17 DEVELOPMENTAL

The study of women working at a metallurgical facility (Belyaeva 1967) also reported decreases in infant body weight gain beginning at 6 months of age; at 12 months of age, they weighed 11% less than infants from the control group. Interpretation of the results of this study is limited by the lack of information on the control group, type of work the women performed, when the workers returned to work after giving birth, and information on confounding exposure to other compounds. A second epidemiological study

evaluated possible associations between urinary antimony levels and birth outcomes in participants of the Longitudinal Investigation of Fertility and the Environment study (Bloom et al. 2015). No associations between maternal or paternal urinary antimony levels and gestational age, birth weight, birth length, head circumference, ponderal index, or newborn sex were found.

A decreased number of offspring was observed in rats exposed to 209 mg Sb/m^3 as antimony trioxide prior to conception and throughout gestation. No difference in fetal body weights was observed (Belyaeva 1967).

A case-control study examined the possible relationship between levels of metals in drinking water and neural tube defects and did not find a significant association for antimony (Longerich et al. 1991). Zheng et al. (2014) found significantly higher median umbilical cord antimony levels in women with adverse pregnancy outcomes, but did not find a statistically significant association between antimony and adverse pregnancy outcomes. See Table 2-1 for more information on these studies.

Decreases in growth on postnatal days (PNDs) 10–22 were observed in the pups of rats exposed to 0.7 mg Sb/kg/day during gestation and lactation (Rossi et al. 1987); a decrease in maternal body weight gain was also observed at these doses. No differences in the number of newborn pups per litter or macroscopic teratogenic effects were observed in the offspring of rats treated during gestation with 0.7 mg Sb/kg/day as antimony trichloride (Rossi et al. 1987).

Studies by Angrisani et al. (1988) and Rossi et al. (1987) (data from both studies were also reported in Marmo et al. 1987) suggest that antimony may interfere with the normal development of the cardiovascular system. Alterations in vasomotor reactivity were observed in 30- and 60-day-old pups exposed during gestation and/or lactation and from weaning to PND 60; the estimated dose during the postnatal period was 0.1 mg Sb/kg/day. However, no alterations in arterial blood pressure were observed. Although the investigators describe this as altered development, comparisons were not made between the vasomotor responses in mature rats and in pups.

Three parenteral studies have evaluated the developmental toxicity of pentavalent antimony. Subcutaneous administration of 300 mg Sb/kg as meglumine antimoniate or intramuscular administration of 100 or 300 mg Sb/kg/day as sodium stibogluconate or meglumine antimoniate to rats during gestation or during gestation and lactation resulted in decreases in birth weight and number of viable offspring (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). Intramuscular administration of

100 mg Sb/kg/day as antimony trichloride also resulted in decreases in viable fetuses and fetal body weight (Alkhawajah et al. 1996). Increases in resorptions were also observed in rats administered ≥100 mg Sb/kg/day as sodium stibogluconate, meglumine antimoniate, or antimony trichloride (Alkhawajah et al. 1996). Miranda et al. (2006) also found a significant increase in dilated ureters following gestation exposure; no other external or visceral abnormalities were found. No alterations in neurological development or sperm counts were observed in offspring exposed during gestation and lactation (Coelho et al. 2014a).

2.18 OTHER NONCANCER

Epidemiological and laboratory animal studies have evaluated several other noncancer effects: diabetes and alterations in blood glucose levels, gout, and spleen damage. Menke et al. (2016) reported an association between urinary antimony levels and the risk of diabetes among NHANES participants. The association was found among all participants and among participants who were current smokers or former smokers, but was not found among never smokers. An association was also found between urinary antimony and homeostatic model assessment of insulin resistance (HOMA-IR); this association was found among all participants and among participants without diabetes (Menke et al. 2016). Two oral exposure studies in rats have reported significant decreases in serum glucose levels following exposure to antimony potassium tartrate. In an intermediate-duration study, dose-related decreases in serum glucose levels were observed in female rats at ≥0.64 mg Sb/kg/day (Poon et al. 1998); the investigators did not report whether blood samples were from fasting or nonfasting rats. ATSDR notes that the serum glucose levels in all groups (including controls) were higher than the normal range reported by the animal supplier (Charles River Laboratories 2006). Decreases in nonfasting glucose were observed in male and female rats exposed for a lifetime to 0.63 mg Sb/kg/day as antimony potassium tartrate (Schroeder et al. 1970); no significant alterations in fasting glucose levels were found. Alterations in blood glucose levels have also been observed in parenteral studies. Significant decreases in blood glucose levels were observed in rats exposed to 900 mg Sb/kg/day as stibogluconate or 300 or 900 mg Sb/kg/day meglumine antimoniate administered via intramuscular injections for 30 days (Alkhawajah et al. 1992); the investigator did not note whether the animals were fasted prior to measurement of blood glucose levels.

Mendy et al. (2012) did not find a significant association between urinary antimony levels and the incidence of self-reported gout among NHANES participants.

Splenic sinus congestion in males at ≥0.56 mg Sb/kg/day, sinus hyperplasia in females at ≥0.64 Sb/kg/day and males at 42.17 Sb/kg/day, and arterial cuff atrophy in males at 42.17 mg Sb/kg/day were observed in rats exposed to antimony potassium tartrate (Poon et al. 1998).

2.19 CANCER

Several studies of antimony oxide workers have examined the carcinogenic potential of antimony. A positive trend in lung cancer deaths with increasing duration of employment was observed in workers at an antimony smelter facility (Schnorr et al. 1995). Similarly, another study of workers exposed to metallic antimony, antimony alloys, and antimony trioxide found increases in lung cancer deaths in workers hired prior to 1940 or between 1946 and 1950 (Jones 1994). In both studies, the workers were also exposed to arsenic and neither study included smoking status as a confounding variable

Four studies have evaluated the carcinogenicity of inhaled antimony trioxide in rats. Increases in lung neoplasms (squamous cell carcinomas, bronchioalveolar adenomas and carcinomas, and scirrhous carcinoma) were observed in female rats exposed to 4.2 mg Sb/m^3 for 55 weeks with a 1-year recovery period (Watt 1983) or 36 mg Sb/m^3 for 52 weeks with a 20-week recovery period (Groth et al. 1986). However, a third study (Newton et al. 1994) did not find any neoplasms in male or female rats exposed to 3.8 mg Sb/m^3 for 1 year with a 1-year recovery period. Newton et al. (1994) stated that a pathologist who examined the slides from the Groth et al. (1986), Watt (1983), and Newton et al. (1994) studies noted more extensive lung damage and a considerable higher amount of antimony trioxide in the lungs of rats tested in the Watt (1983) study as compared to those tested in the Newton et al. (1994) study even though the concentrations were similar, suggesting that the actual concentrations tested by Watt (1983) may have been higher than reported. A fourth study found significant increases in the incidence of alveolar/bronchiolar adenomas at 8.3 mg Sb/m^3 and benign pheochromocytomas in the adrenal gland of rats exposed to 25 mg Sb/m^3 for 2 years (NTP 2016). Increases in lung neoplasms were also observed in rats exposed to 17.5 mg Sb/m^3 as antimony ore for 52 weeks followed by a 1-year recovery period (Groth et al. 1986). In mice, a 2-year exposure to antimony trioxide resulted in significant increases in alveolar/bronchiolar adenomas, carcinomas, or combined incidences at ≥2.5 mg Sb/m^3, malignant lymphomas in females exposed to ≥2.5 mg Sb/m^3, and fibrous histiocytomas in the skin of males exposed to 25 mg Sb/m^3 (NTP 2016). No increases in lung tumors were observed in pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide (Watt 1983).

Three epidemiology studies evaluated the possible association between antimony and cancer incidence associated with environmental exposure (see Table 2-1). Colak et al. (2015) found an association between antimony levels in drinking water samples and cancer incidence among populations of three Turkish cities; the antimony levels in the water were <20 μg/L. Guo et al. (2016) and Mendy et al. (2012) did not find associations between urinary antimony levels and self-reported cancer among adult NHANES participants; Guo et al. (2016) also did not find an association with cancer deaths.

No alterations in neoplastic lesion incidence were observed in rats (Schroeder et al. 1970) or mice (Kanisawa and Schroeder 1969) orally exposed 0.63 or 0.35 mg Sb/kg/day, respectively, as antimony potassium tartrate in drinking water for a lifetime. The use of these studies to assess carcinogenicity is limited because only one exposure level was used, which was below the maximum tolerated dose.

HHS (NTP 2018) categorized antimony trioxide as reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from experimental animal studies and supporting mechanistic data. IARC (2015) has determined that antimony trioxide is possibly carcinogenic to humans (Group 2B) and antimony trisulfide is not classifiable as to carcinogenicity in humans (Group 3). The EPA has not evaluated the carcinogenicity of antimony.

2.20 GENOTOXICITY

The genotoxicity of trivalent and pentavalent antimony has been evaluated in *in vivo* studies in humans, rats, and mice and in *in vitro* studies in bacterial and mammalian systems. No alterations in micronuclei formation in reticulocytes or DNA damage in leukocytes or lung tissue (see Table 2-6) were observed in rats chronically exposed via inhalation to antimony trioxide (NTP 2016). In contrast, a similar exposure in mice resulted in increases in micronuclei formation in micronucleated mature erythrocytes (no alterations were found in reticulocytes) and increases in DNA damage in lung tissue (no alterations in leukocytes) (NTP 2016). As summarized in Table 2-6, most studies of antimony trioxide did not find clastogenic alterations in orally exposed (gavage administration) rats or mice (Elliott et al. 1998; Gurnani et al. 1992a, 1992b; Kirkland et al. 2007). One study (Gurnani et al. 1992a, 1993) found significant increases in chromosomal aberrations in mice bone marrow cells following repeated exposure to antimony trioxide; no significant alterations were found following a single exposure. However, other studies testing similar doses did not find increases in chromosomal aberrations (Kirkland et al. 2007) or micronuclei formation (Elliott et al. 1998; Kirkland et al. 2007) following repeated exposure. One occupational exposure study of workers exposed to a flame retardant containing antimony trioxide did not

find increases in the occurrence of micronuclei or sister chromatid exchange (Cavallo et al. 2002). Two studies of pentavalent organic antimony found positive results for micronuclei formation (Hantson et al. 1996; Lima et al. 2010) or DNA damage (Lima et al. 2010). A study of NHANES participants found an inverse association between telomer length and urinary antimony levels (Scinicariello and Buser 2016); when the participants were categorized by age, the associations were found in participants 40–85 years of age.

Table 2-6. Genotoxicity of Antimony *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Mouse bone marrow; single exposure (gavage)	Chromosomal aberrations	–	Gurnani et al. 1992a, 1992b	Antimony trioxide
Mouse bone marrow; 7–21 exposures (gavage)	Chromosomal aberrations	+	Gurnani et al. 1992a, 1993	Antimony trioxide
Rat bone marrow; single exposure (gavage)	Chromosomal aberrations	–	Kirkland et al. 2007	Antimony trioxide
Rat bone marrow; 7–21 exposures (gavage)	Chromosomal aberrations	–	Kirkland et al. 2007	Antimony trioxide
Human peripheral lymphocytes (intramuscular)	Chromosomal aberrations	–	Hantson et al. 1996	Meglumine antimonate
Human peripheral lymphocytes (inhalation)	Micronuclei formation	–	Cavallo et al. 2002	Antimony trioxide
Human peripheral lymphocytes (intramuscular)	Micronuclei formation	+	Hantson et al. 1996	Meglumine antimonate
Rat reticulocytes 12-month exposure (inhalation)	Micronuclei formation	–	NTP 2016	Antimony trioxide
Mouse reticulocytes 12-month exposure (inhalation)	Micronuclei formation	–	NTP 2016	Antimony trioxide
Mouse micronucleated mature erythrocytes 12-month exposure (inhalation)	Micronuclei formation	+	NTP 2016	Antimony trioxide
Mouse bone marrow (gavage)	Micronuclei formation	+	Lima et al. 2010	N-Methyl-glucamine antimonate
Mouse bone marrow; single exposure (gavage)	Micronuclei formation	–	Elliott et al. 1998	Antimony trioxide
Mouse bone marrow; 7–21 exposures (gavage)	Micronuclei formation	–	Elliott et al. 1998	Antimony trioxide
Rat bone marrow; single exposure (gavage)	Micronuclei formation	–	Kirkland et al. 2007	Antimony trioxide
Rat bone marrow; 7–21 exposures (gavage)	Micronuclei formation	–	Kirkland et al. 2007	Antimony trioxide
Human peripheral lymphocytes (inhalation)	Sister chromatid exchange	–	Cavallo et al. 2002	Antimony trioxide

Table 2-6. Genotoxicity of Antimony *In Vivo*

Species (test system)	Endpoint	Results	Reference	Compound
Human peripheral lymphocytes (intramuscular)	Sister chromatid exchange	–	Hantson et al. 1996	Meglumine antimonate
Rat leukocytes 12-month exposure (inhalation)	DNA damage (comet assay)	–	NTP 2016	Antimony trioxide
Rat lung tissue samples 12-month exposure (inhalation)	DNA damage (comet assay)	–	NTP 2016	Antimony trioxide
Mouse leukocytes 12-month exposure (inhalation)	DNA damage (comet assay)	–	NTP 2016	Antimony trioxide
Mouse lung tissue samples 12-month exposure (inhalation)	DNA damage (comet assay)	+	NTP 2016	Antimony trioxide
Mouse peritoneal macrophages (gavage)	DNA damage	+	Lima et al. 2010	N-Methyl-glucamine antimonate
Rat liver (gavage)	DNA repair	–	Elliott et al. 1998	Antimony trioxide
Mouse sperm (gavage)	Sperm head abnormalities	–	Gurnani et al. 1992a, 1993	Antimony trioxide

– = negative result; + = positive result; DNA = deoxyribonucleic acid

The results of *in vitro* genotoxicity studies are presented in Table 2-7. In general, no alterations in the occurrence of gene mutations were found in bacterial assays testing metallic antimony (Asakura et al. 2009), antimony trioxide (Elliott et al. 1998; Kuroda et al. 1991), antimony trichloride (Kubo et al. 2002; Kuroda et al. 1991), antimony pentachloride (Kuroda et al. 1991), or antimony pentoxide (Kuroda et al. 1991) or in mammalian assays with antimony thioantimonate (Tu and Sivak 1984) or antimony trioxide (Elliott et al. 1998). Evidence of DNA damage was observed for antimony trioxide, antimony trichloride, and antimony pentachloride in rec assays with *Bacillus subtilis* (Kanematsu et al. 1980; Kuroda et al. 1991). Unlike the *in vivo* data, most studies found increases in the occurrence of chromosomal aberrations (Asakura et al. 2009; Elliott et al. 1998; Paton and Allison 1972; Tu and Sivak 1984), micronuclei formation (Gebel et al. 1998a; Huang et al. 1998; Migliore et al. 1999; Schaumlöffel and Gebel 1998), and sister chromatid exchange (Kuroda et al. 1991) in mammalian cells exposed to trivalent antimony compounds or metallic antimony. Pentavalent antimony compounds were negative in sister chromatid exchange assays (Kuroda et al. 1991). Similarly, DNA damage was observed in mammalian cells exposed to antimony trichloride (Gebel et al. 1998a; Kopp et al. 2018; Schaumlöffel and Gebel 1998), but negative for pentavalent organic antimony (Lima et al. 2010); evidence of impaired repair of DNA double strand breaks was also observed for antimony trichloride (Koch et al. 2017).

Table 2-7. Genotoxicity of Antimony *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Prokaryotic organisms					
Salmonella typhimurium TA100, TA1535, TA98, TA1537	Gene mutation (reverse mutation)	–	+[a]	Asakura et al. 2009	Metallic antimony
S. typhimurium TA100, TA1535, TA1537, TA98	Gene mutation (plate incorporation)	–	–	Elliott et al. 1998	Antimony trioxide
S. typhimurium TA100, TA98	Gene mutation (plate incorporation)	–	–	Kuroda et al. 1991	Antimony trioxide
S. typhimurium TA100, TA98	Gene mutation (Ames test)	–	–	Kubo et al. 2002	Antimony trichloride
S. typhimurium TA100, TA98	Gene mutation (plate incorporation)	–	–	Kuroda et al. 1991	Antimony trichloride
S. typhimurium TA100, TA1535, TA97, TA98	Gene mutation	–	–	Zeiger et al. 1992; NTP 1992	Antimony potassium tartrate
S. typhimurium TA100, TA98	Gene mutation (plate incorporation)	–	–	Kuroda et al. 1991	Antimony pentachloride
S. typhimurium TA100, TA98	Gene mutation (plate incorporation)	–	–	Kuroda et al. 1991	Antimony pentoxide
Escherichia coli WP2uvrA/pKM101	Gene mutation (reverse mutation)	–	–	Asakura et al. 2009	Metallic antimony
E. coli WP2P, WP2PuvrA	Gene mutation (plate incorporation)	–	–	Elliott et al. 1998	Antimony trioxide
E. coli PQ37	Gene mutation (SOS chemotest)	No data	–	Lantzsch and Gebel 1997	Antimony trichloride
Bacillus subtilis	DNA damage (rec assay)	No data	+	Kuroda et al. 1991	Antimony trioxide
B. subtilis	DNA damage (rec assay)	No data	+	Kanematsu et al. 1980	Antimony trioxide
B. subtilis	DNA damage (rec assay)	No data	+	Kanematsu et al. 1980	Antimony trichloride
B. subtilis	DNA damage (rec assay)	No data	+	Kuroda et al. 1991	Antimony trichloride
B. subtilis	DNA damage (rec assay)	No data	+	Kuroda et al. 1991 (	Antimony pentachloride
B. subtilis	DNA damage (rec assay)	No data	+	Kanematsu et al. 1980	Antimony pentachloride
B. subtilis	DNA damage (rec assay)	No data	–	Kuroda et al. 1991	Antimony pentoxide

Table 2-7. Genotoxicity of Antimony *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
Mammalian cells					
Chinese hamster ovary cells (HGPRT locus)	Gene mutation	–	–	Tu and Sivak 1984	Antimony thioantimonate
L5178Y mouse lymphoma	Gene mutation	–	–	Elliott et al. 1998	Antimony trioxide
Human leukocytes	Chromosomal aberrations	No data	+	Paton and Allison 1972	Antimony sodium tartrate
Human leukocytes	Chromosomal aberrations	+	+	Elliott et al. 1998	Antimony trioxide
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Asakura et al. 2009	Metallic antimony
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Tu and Sivak 1984	Antimony thioantimonate
Human bronchial epithelial cells (BES-6)	Micronuclei formation	No data	+	Huang et al. 1998	Antimony trichloride
Human fibroblasts	Micronuclei formation	No data	+	Huang et al. 1998	Antimony trichloride
Human lymphocytes	Micronuclei formation	No data	+	Schaumlöffel and Gebel 1998	Antimony trichloride
Human lymphocytes	Micronuclei formation	No data	+	Migliore et al. 1999	Potassium antimonate
V79 Chinese hamster cells	Micronuclei formation	No data	+	Gebel et al. 1998a	Antimony trichloride
Chinese hamster ovary cells	Micronuclei formation	No data	+	Huang et al. 1998	Antimony trichloride
V79 Chinese hamster ovary cells	Sister chromatid exchange	No data	+	Kuroda et al. 1991	Antimony trichloride
V79 Chinese hamster ovary cells	Sister chromatid exchange	No data	+	Kuroda et al. 1991	Antimony trioxide
V79 Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Kuroda et al. 1991	Antimony pentachloride
V79 Chinese hamster ovary cells	Sister chromatid exchange	No data	–	Kuroda et al. 1991	Antimony pentoxide
Human lymphocytes	DNA damage (comet assay)	No data	+	Schaumlöffel and Gebel 1998	Antimony trichloride
Human lymphocytes	DNA damage (comet assay)	No data	–	Lima et al. 2010	N-Methyl-glucamine antimonate
HepG2 cells (human cell line)	DNA damage (γH2AX ICW assay)	No data	+	Kopp et al. 2018	Antimony trichloride

Table 2-7. Genotoxicity of Antimony *In Vitro*

Species (test system)	Endpoint	Results		Reference	Compound
		With activation	Without activation		
LS-174T cells (human cell line)	DNA damage (γH2AX ICW assay)	No data	+	Kopp et al. 2018	Antimony trichloride
V79 Chinese hamster cells	DNA damage (comet assay)	No data	+	Gebel et al. 1998a	Antimony trichloride
HeLa S3 cells	DNA repair (double strand break)	No data	+	Koch et al. 2017	Antimony trichloride

[a]Only positive for TA1537 strain.

– = negative result; + = positive result

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- Antimony is poorly absorbed and its absorption is strongly influenced by the administered antimony compound. Poorly soluble compounds such as antimony trioxide are slowly cleared from the lungs (measured in weeks) compared to more soluble compounds, such as antimony trichloride, which are cleared from the lungs in days. Absorption through the gastrointestinal tract is estimated at approximately 1% for antimony trioxide and 10% for antimony potassium tartrate.

- Antimony is distributed throughout the body with the highest concentrations in the lungs, gastrointestinal tract, red blood cells, liver, kidney, bone, spleen, and thyroid.

- Antimony is not metabolized. However, there are data suggesting the interconversion of pentavalent antimony and trivalent antimony.

- Antimony is excreted in the urine and feces. Trivalent antimony is predominantly excreted in the feces, with smaller amounts in the urine and pentavalent antimony is primarily excreted in the urine.

3.1.1 Absorption

Inhaled antimony particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption into blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, liver, kidney). The above processes apply to all forms of deposited antimony, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size, solubility).

Particles having diameters >5 μm deposit in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract. Smaller particles (≤5 μm, *respirable* particles) are deposited primarily in the pulmonary region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by absorption, lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow. Total alveolar clearance is mediated largely by alveolar macrophages, primarily via migration of particle-laden macrophages to the ciliated airways and to a lesser extent via penetration through the interstitium to the pulmonary lymphatic system (Yu and Rappaport 1996). Exposure to 1.6 μm particles of antimony tartrate resulted in a greater deposition of antimony in the upper respiratory tract than exposure to 0.7 or

0.3 μm particles (Felicetti et al. 1974a; Thomas et al. 1973). Furthermore, the antimony deposited in the upper respiratory tract was cleared after several hours via mucociliary clearance. Particles of the two smaller sizes were relatively insoluble in the lung and were slowly absorbed over several weeks (Thomas et al. 1973). No valence-specific difference in the body burden was observed 1 day after exposure to trivalent or pentavalent antimony tartrate (Felicetti et al. 1974b).

Dissolved antimony is absorbed into blood; the rate of absorption will depend on solubility. The International Commission on Radiological Protection (ICRP 1981) considers oxides, hydroxides, halides, sulfides, sulfates, and nitrates of antimony to be class W chemicals. All other common compounds of antimony are assigned to class D. Class W and D chemicals are considered to have respiratory tract clearance rates of weeks and days, respectively. The ICRP classifications are based on animal data (Felicetti et al. 1974a, 1974b; Thomas et al. 1973). Data from deceased antimony smelter workers suggest that the elimination half-times of some forms of antimony in the lungs may be longer than weeks (Gerhardsson et al. 1982).

Using data from the Newton et al. (1994) 1-year study of rats exposed to several concentrations of antimony trioxide, Yu and Rappaport (1996) and Newton et al. (1994) found that the pulmonary clearance half-time increased with increasing antimony lung burdens. Clearance was significantly decreased at lung burdens of >0.11 mg (Yu and Rappaport 1996). In rats exposed to antimony trioxide for 1 year, Newton et al. (1994) estimated a pulmonary clearance time of 2 months in rats with a lung burden of 200 μg and 10 months in rats with a lung burden of 2,000 μg. In rats exposed to 0.06, 0.51, or 4.50 mg antimony trioxide/m^3 (ratio of 1:10:90), the lung burden ratios were 1:11:138. The decrease in clearance rates is likely due to antimony-specific impairment of alveolar macrophages (Yu and Rappaport 1996). As would be expected, lung burdens increased with exposure duration. In rats exposed for 90 days, there was an initial rapid accumulation phase, which lasted 2–4 weeks, followed by a second slower accumulation phase; there was no indication that lung accumulation reached steady state. However, a 1-year study showed that steady-state lung burden was reached after approximately 6 months of exposure to antimony trioxide (Newton et al. 1994).

Results of studies in animals suggest that antimony is poorly absorbed from the gastrointestinal tract. Estimates of the absorption of antimony tartrate and antimony trichloride in animals range from 2 to 7% (Felicetti et al. 1974b; Gerber et al. 1982). A study of pentavalent antimony estimated a bioavailability of 10% in dogs administered via gavage a single dose of 100 mg Sb/kg as meglumine antimoniate (Ribeiro et al. 2010); the mean absorption time was 3.1 hours. Gastrointestinal absorption of antimony is likely to

be affected by numerous factors, including chemical form and solubility of the ingested antimony, age, and diet. Although quantitative information on the absorption of antimony is not available for all forms, ICRP (1981) has recommended 10% for antimony tartrate and 1% for all other forms of antimony as reference values for gastrointestinal absorption in humans. A dog study (Ribeiro et al. 2010) showed that maximum blood concentration was reached 0.89 hours after gavage administration of 100 mg Sb/kg as meglumine antimoniate.

The gastrointestinal absorption of antimony may be saturable. A comparison of blood concentrations 24 hours after administration of 100 or 1,000 mg/kg antimony trioxide found only a 2-fold difference, even though there was a 10-fold difference in doses (Kirkland et al. 2007).

Exposure to high levels of antimony trioxide or a mixture of antimony trioxide and pentoxide resulted in death in rabbits (Myers et al. 1978). Since the application area was occluded, the study suggests that at least some forms of antimony can be absorbed through the skin.

There are very limited data on pharmacokinetic mechanisms. Maciaszczyk-Dubinska et al. (2012) suggested that trivalent antimony can enter the cell via aquaglyceroporins, which are membrane proteins, because trivalent antimony in the trihydroxylated uncharged form resembles glycerol. There is also some evidence that trivalent antimony can enter the cell via hexose transporters. Sun et al. (2000) suggested that trivalent antimony forms a stable complex with glutathione, which provides a possible transport mechanism.

3.1.2 Distribution

Very low levels of antimony are found in unexposed humans. Autopsy data on Japanese adults (Sumino et al. 1975) and other data on selected body fluids are presented in Table 3-1. The mean body burden of antimony was 0.7 mg (Sumino et al. 1975). The skin and hair had the highest levels of antimony. A somewhat higher estimate of 7.9 mg for total body burden is reported by ICRP (1981). ICRP (1981) has recommended reference values of 5.9 mg of antimony in soft tissue and 2.0 mg in skeletal tissue.

Table 3-1. Background Levels of Antimony Found in Various Tissues of Humans

Tissue	Mean concentration (µg/g) ± standard deviation	Reference
Hair	0.12±0.18	Muramatsu and Parr 1988
	0.096	Takagi et al. 1986
Adrenal gland	0.073±0.14	Sumino et al. 1975
Skin	0.096±0.10	Sumino et al. 1975
Lung	0.062±0.056	Sumino et al. 1975
Large intestine	0.047±0.062	Sumino et al. 1975
Trachea	0.045±0.031	Sumino et al. 1975
Cerebellum	0.030±0.032	Sumino et al. 1975
Kidney	0.043±0.041	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Small intestine	0.039±0.044	Sumino et al. 1975
Heart	0.032±0.038	Sumino et al. 1975
Pancreas	0.030±0.029	Sumino et al. 1975
Spleen	0.029±0.025	Sumino et al. 1975
Liver	0.023±0.026	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Cerebrum	0.017±0.024	Sumino et al. 1975
Blood	0.016±0.022	Sumino et al. 1975
	0.34±2.0	Mansour et al. 1967

The highest concentrations of antimony are found in the lungs (inhalation exposure), gastrointestinal tract, red blood cells, liver, kidney, bone, lung (oral exposure), spleen, and thyroid of laboratory animals exposed via inhalation or oral exposure (Ainsworth et al. 1991; Felicetti et al. 1974b; Kirkland et al. 2007; NTP 1992; Poon et al. 1998; Sunagawa 1981). Studies involving exposure to antimony trioxide, a relatively insoluble compound, demonstrate that most antimony is retained in the lungs (Newton et al. 1994). In parenteral studies, antimony is recovered primarily in the liver and thyroid, with smaller amounts in the spleen, heart, lungs, and muscle (Friedrich et al. 2012; Gellhorn et al. 1946; Gerber et al. 1982). Poon et al. (1998) reported apparent dose-related increases in kidney, liver, spleen, and red blood cell antimony levels in rats orally exposed to antimony potassium tartrate for an intermediate duration. However, two other oral studies did not report dose-related increases in tissue antimony levels (NTP 1992; Sunagawa 1981). This lack of dose-responsiveness may be a reflection of decreased absorption at higher antimony concentrations or may represent saturation in some tissues. Antimony levels tend to reach a plateau in the livers and lungs of voles fed a diet containing antimony trioxide (Ainsworth et al. 1991). In rats exposed to antimony potassium tartrate in drinking water for 16 days (NTP 1992) or 13 weeks (Poon et al. 1998) or antimony trioxide once or 3 times in an 8-day period (Kobayashi and Ogra 2009), the blood had the highest concentration of antimony. The antimony levels in blood were 3 times

higher than the levels in the kidney, heart, spleen, and liver (NTP 1992). The clearance of antimony from the blood appears to differ among animal species. Elevated blood antimony levels persist longer in rats than in mice and dogs (Felicetti et al. 1974a; Thomas et al. 1973).

A series of studies conducted by Paßlack and associates examined the liver and kidney levels of antimony in animals exposed to background levels of antimony. No differences between liver and kidney antimony concentrations were found in dogs and cats (Paßlack et al. 2014b, 2014c); in contrast, liver antimony levels were significantly higher than kidney levels in horses (Paßlack et al. 2014a). No sex- or age-related differences in antimony concentrations were found (Paßlack et al. 2014a, 2014b, 2014c). In dogs and cats, chronic kidney disease did not appear to influence the antimony levels in the liver or kidneys (Paßlack et al. 2014b, 2014c).

Several studies have evaluated differences in the distribution of trivalent and pentavalent antimony. In hamsters exposed to airborne antimony tartrate, the levels of trivalent antimony increase more rapidly in the liver than pentavalent antimony. Skeletal uptake is greater following exposure to pentavalent antimony than trivalent antimony (Felicetti et al. 1974b). One day postexposure, the highest percentage of body burden is found in the gastrointestinal tract. Following exposure to trivalent antimony tartrate, antimony is also retained in the skin, liver, skeleton, and lung (in descending order). For pentavalent antimony, the highest percentage of body burden (outside of gastrointestinal tract) is skin, skeleton, and liver. A study of rats exposed to similar concentrations of metallic antimony and antimony trioxide also found some distribution differences (Sunagawa 1981). Exposure to metallic antimony resulted in similar antimony concentrations in the liver and blood of rats; in contrast, antimony trioxide exposure resulted in a 10-fold higher concentration in the blood than in the liver.

Following intraperitoneal administration of trivalent antimony compounds, the concentration of antimony in the liver exceeded the antimony concentration in the spleen (Gellhorn and van Dyke 1946). In contrast, administration of pentavalent antimony compounds resulted in spleen concentrations that exceeded the liver concentration. Similarly, a 21-day subcutaneous administration of 300 mg Sb/kg as meglumine antimoniate (pentavalent antimony) to rats resulted in the highest antimony concentrations in the spleen; high levels were also found in the kidneys, femur, thyroid, and liver (Coelho et al. 2014b). The antimony concentration in the spleen was at least 4–5 times higher than in other tissues; the concentrations in the kidneys, femur, and thyroid were similar and about 2 times higher than in the liver. Twenty-one days after the last exposure, the highest concentration was found in the spleen followed by the femur and thyroid (similar concentrations), lungs, adrenals, kidneys, and liver (Coelho et al. 2014b).

In contrast, intraperitoneal administration of antimony potassium tartrate (1.5–11 mg/kg/day) to rats for 16 days resulted in the highest antimony concentration in the blood, followed by the liver, spleen, heart, and kidney (NTP 1992). At the lower doses, the liver and spleen had similar concentrations, which were 2 times higher than the heart and kidney levels. Following a 13-week exposure to 24 mg/kg/day, the blood antimony concentration was >2 times higher than the spleen levels; the spleen had 20% more antimony than the liver, and the heart and kidney had similar concentrations that were approximately 10-fold lower than blood.

In the blood, pentavalent antimony is primarily found in the serum (Edel et al. 1983; Felicetti et al. 1974b; Ribeiro et al. 2010) and trivalent antimony was found primarily in the red blood cells, mainly in the hemoglobin fraction (Edel et al. 1983; Kobayashi and Ogra 2009; Lippincott et al. 1947; Newton et al. 1994; Poon et al. 1998). In hamsters, the ratios of erythrocyte to plasma antimony levels were 1.14 for trivalent antimony and 0.29 for pentavalent antimony at exposure termination and 8.1 and 2.9, respectively, 1-day postexposure (Felicetti et al. 1974b). *In vitro* studies found that pentavalent antimony can pass through the erythrocyte membrane via protein channels (Barrera et al. 2016; Quiroz et al. 2013).

There are limited data on the maternal transfer of antimony. A study of pregnant women in Bolivia found a significant correlation between antimony levels in maternal blood and levels in cord blood (Barbieri et al. 2016). Elevated antimony levels were found in the pups of rat dams fed radiolabeled antimony chloride (exact compound not reported) during pregnancy and lactation (Gerber et al. 1982). The highest activities (in descending order) were detected in the bone, muscle, spleen, heart, kidney, and lung. After exposure termination, antimony levels rapidly declined, with a half-life of approximately 10 days. When *in utero* exposed pups were cross-fostered to controls, antimony levels were maintained. In control newborns cross-fostered to antimony dams, there was a rapid increase in antimony level, reaching 80% of the levels of pups exposed during gestation and lactation. A series of experiments in which rat dams were administered subcutaneous injections of 300 mg pentavalent Sb/kg/day as meglumine antimoniate during gestation and/or lactation demonstrates maternal-fetal and maternal-infant transfer of antimony (Coelho et al. 2014a). The levels of antimony in the blood of the offspring were approximately 44, 60, 77, and 135% of maternal blood levels when antimony was administered on gestation days (GDs) 0–20, GD 0 through PND 13, PNDs 1–13, and PNDs 5–19, respectively.

3.1.3 Metabolism

Antimony is a metal and, therefore, does not undergo metabolism. Antimony can covalently interact with sulfhydryl groups and phosphate, as well as numerous reversible binding interactions with endogenous ligands (e.g., proteins). It is not known if these interactions are toxicologically significant.

There are limited data on the *in vivo* conversion of pentavalent antimony to trivalent antimony. In humans administered Ulamina (an experimental drug containing antimony pentachloride and N-methyl-glucamine) via intramuscular injection, 23% of the pentavalent antimony was converted to trivalent antimony (Vasquez et al. 2006). A study in monkeys administered the pentavalent antimony compound, meglumine antimoniate, reported that the proportion of trivalent antimony in the plasma increased from 5% on exposure day 1 to 50% on exposure day 9; the plasma levels of pentavalent antimony remained constant (11–20%) during this time period (Friedrich et al. 2012). An *in vitro* study in human blood demonstrated the reduction of pentavalent antimony to trivalent antimony in the presence of glutathione (Lopez et al. 2015). In contrast to these findings in blood, Wyllie and Fairlamb (2006) reported that differences in the toxicity of pentavalent antimony and trivalent antimony to macrophages suggested that pentavalent antimony was not reduced to trivalent antimony in macrophages.

3.1.4 Excretion

There are limited information on antimony excretion following inhalation, oral, or dermal exposure. Increased levels of urinary antimony have been noted in workers exposed to antimony trioxide (Cooper et al. 1968; Ludersdorf et al. 1987). In animals, inhaled antimony is excreted via the urine and feces. Some of the fecal antimony may represent unabsorbed antimony that is cleared from the lung via mucociliary action into the esophagus to the gastrointestinal tract. The whole-body clearance of trivalent or pentavalent antimony tartrate in hamsters is biphasic. One day postexposure, 65 and 60% of the initial body burden of trivalent and pentavalent antimony, respectively, was excreted (Felicetti et al. 1974b). The half-life of the slow phase was approximately 16 days. The investigators suggested that the pentavalent antimony was likely converted to trivalent antimony, which could explain the similar excretion patterns. Based on the results of a study in which hamsters received a single gavage dose of trivalent or pentavalent antimony tartrate, antimony appears to be excreted rapidly with a half-life of <1 day (Felicetti et al. 1974b).

Information obtained from human and animal studies in which antimony was administered parenterally provides some insight regarding the routes and rates of excretion that can be anticipated after oral exposure in humans. Antimony absorbed from the gastrointestinal tract appears to be excreted in the urine and feces to a variable degree, depending on the chemical form. Pentavalent antimony is rapidly excreted in humans following intravenous or intramuscular administration, with >50% excreted in the urine 6 hours after injection (Goodwin and Page 1943; Rees et al. 1980). Trivalent antimony is predominantly excreted in the feces and not as rapidly excreted in the urine as pentavalent antimony. Twenty-four hours after injection, approximately 25% was excreted in the urine (Goodwin and Page 1943).

Following repeated intramuscular administration of trivalent antimony in humans, approximately 15% was excreted per day at the beginning of treatment and 25% at the end of treatment. Fecal antimony excretion ranged from 4% in the beginning of treatment to 15.4% of the daily administered dose toward the end of treatment (Lippincott et al. 1947). Twenty-four hours following intraperitoneal administration of trivalent antimony in rats, 33% of the compound was excreted via the feces and 6% in the urine. In contrast, 88% of the pentavalent antimony was excreted in the urine and 1% in the feces (Edel et al. 1983). Another study found that 45–55% of the antimony administered via intravenous or intraperitoneal administration of antimony trichloride was excreted in the urine or feces within 4 days (Bailly et al. 1991).

Route-specific differences in the excretion routes were found. Following intraperitoneal injection, the amount of antimony in the feces was 4 times higher than the amount in the urine; in contrast, the amount in urine and feces was similar when administered via intravenous administration. Antimony was partially excreted in the bile likely bound to glutathione; some of the biliary antimony was reabsorbed in the intestine via enterohepatic circulation (Bailly et al. 1991).

The elimination of pentavalent antimony following intramuscular injection fits into a two-compartment pharmacokinetic model. The half-life of the rapid phase of elimination was 2 hours (Chulay et al. 1988; Vasquez et al. 2006); the slower phase was 76 hours (Chulay et al. 1988). A more recent study that had a lower detection limit suggested that antimony elimination fits a three-compartment model; the terminal half-life was >30 days (Friedrich et al. 2012).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models for antimony were identified.

3.1.6 Animal-to-Human Extrapolations

Overall, the available human and laboratory animal data suggest that the endpoints of antimony toxicity are similar across species. The primary effects observed in antimony workers are respiratory effects such as pneumoconiosis and evidence of heart damage. Lung damage is the primary effect reported in rats, mice, and rabbits exposed to airborne antimony trioxide. Additionally, parenteral administration studies in laboratory animals have found EKG alterations, which is a commonly reported side effect in humans receiving repeated injections of antimony compounds, particularly trivalent compounds, for the treatment of leishmaniasis. Although similar endpoints have been identified, there are limited data comparing the potency across species of antimony administered via environmentally relevant routes of exposure. NTP (2016) found species differences in the toxicity and carcinogenicity of antimony trioxide. Although rats and mice were exposed to the same concentrations, alveolar/bronchiolar carcinomas were observed in mice exposed to ≥2.5 mg Sb/m^3, but carcinomas were not observed in rats exposed to 2.5 or 25 mg Sb/m^3. This study also found differences in lung burdens between rats and mice. In rats, lung burdens appeared to reach steady state at lower concentrations (2.5 and 8.3 mg Sb/m^3); lung burden steady state was not reached at any of the exposure concentrations in mice. In an NTP (1992) 13-week intraperitoneal injection study, antimony potassium tartrate was more toxic in rats than mice. Increases in mortality and hepatocellular degeneration and necrosis were observed in rats; no deaths or histopathological alterations were observed in mice administered the same dosages.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to antimony are discussed in Section 5.7, Populations with Potentially High Exposures.

No studies are available comparing the toxicity of antimony in adults and children. The health effects observed in adults are presumed to also occur in children. The developmental toxicity of antimony in laboratory animals has been assessed in an inhalation study (Belyaeva 1967), an oral study (Rossi et al. 1987), and parenteral studies (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). A decrease in litter size was observed in rats exposed to 209 mg Sb/m^3 as antimony trisulfide 4 hours/day for 1.5–2 months; no alterations in birth weight or pup body weights on PND 21 were found (Belyaeva 1967). In contrast, an oral exposure study (Rossi et al. 1987) reported no alterations in litter size in the offspring of rats exposed to 0.7 mg Sb/kg/day as antimony trichloride during gestation and lactation; however, significant decreases in pup body weight on PNDs 10–60 were found. Decreases in litter size, fetal body weight, and birth weight were observed in rats injected with meglumine antimoniate, sodium stibogluconate, or antimony trioxide during gestation (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). This study also provided evidence of transplacental transfer of antimony. Elevated antimony levels were found in fetal blood; the levels were 70% of those found in the dams (Miranda et al. 2006). However, gestation and lactational exposure to meglumine antimoniate resulted in blood antimony levels in pups that exceeded maternal blood levels (Coelho et al. 2014a).

A study by Cruz et al. (2007) compared plasma antimony levels in children (aged 2–7 years) to those of adults following intramuscular injections of 20 mg Sb/kg as meglumine antimoniate for 20 days for the treatment of leishmaniasis. The plasma antimony concentrations were significantly lower in children compared to adults and a significantly shorter elimination half-life was estimated in the children (1.48 hours) compared to the adults (1.99 hours).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to antimony are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for antimony from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by antimony are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Elevated blood, urine, and fecal levels of antimony indicate high exposure to antimony. Factory workers exposed to antimony trioxide (0.042–0.70 mg Sb/m^3) had elevated urine and blood antimony levels (Ludersdorf et al. 1987). Antimony levels in the urine and blood were 1.1 and 0.9–5.0 μg/L, respectively, compared to 0.6 μg/L urine levels and 0.4 μg/L blood levels in unexposed workers. Another study of workers producing antimony pentoxide and sodium antimoniate found significant correlations between airborne antimony levels and urinary antimony levels, particularly if the air levels were compared to postshift increases in urinary levels (Bailly et al. 1991). A second study found correlations between antimony levels in air (workers exposed to antimony trioxide or sodium antimonite) and blood, urine, and hair antimony levels (correlation coefficients of 0.713, 0.870, and 0.865, respectively) (Wu and Chen 2017). A study evaluating the variability of urinary antimony levels in healthy adults found poor reproducibility in urinary levels measured over several days or several months (Wang et al. 2019). The investigators estimated that at least five urinary samples would be need to accurately estimate an individual's exposure level. There is limited information that hair antimony may also be a biomarker of exposure. A significant correlation was found between the level of pentavalent antimony (N-methylglucamine antimonate) administered intraperitoneally to humans and antimony levels in hair (Dorea et al. 1989). However, Dorea et al. (1989) only tested two levels of antimony (10 and 20 mg Sb/kg/day). Hair antimony levels have not been established as a reliable biomarker of internal antimony exposure.

3.3.2 Biomarkers of Effect

No toxic symptoms specific to antimony exposure have been identified. Toxic effects that reportedly occur in humans include pneumoconiosis, altered EKG readings, and gastrointestinal effects. No quantitative biomarkers associated with these effects are known.

3.4 INTERACTIONS WITH OTHER CHEMICALS

No information on the influence of other compounds on the toxicity of inhaled or ingested antimony was located.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Antimony (Sb) is in the fourth row of group 5A (IUPAC group 15) in the periodic table, residing between arsenic and bismuth. Antimony displays four oxidation states: -3, 0, +3, and +5. The most common and stable oxidation states of antimony in aqueous solutions and biological fluids are Sb(III) and Sb(V). Antimony is sometimes referred to as a metalloid, indicating that it displays both metallic and nonmetallic characteristics (Li 2011).

Table 4-1 lists the common synonyms, trade names, and other pertinent identification information for antimony and selected antimony compounds.

Table 4-1. Chemical Identity of Antimony and Compounds[a]

Characteristic	Information		
Chemical name	Antimony	Antimony pentasulfide	Antimony pentoxide
Synonym(s)	Antimony black; stibium, antimony regulus	Antimonial saffron; antimonic sulfide; antimony red; antimony; golden antimony sulfide, antimony persulfide[c]	Antimonic oxide; antimony pentaoxide; diantimony pentoxide; stibic anhydride; antimonic anhydride; antimonic acid[c]
Registered trade name(s)	No data	No data	No data
Chemical formula	Sb[b]	S_5Sb_2[d]	O_5Sb_2[d]
Chemical structure	Sb	No data	No data
CAS Registry Number	7440-36-0	1315-04-4	1314-60-9

Table 4-1. Chemical Identity of Antimony and Compounds[a]

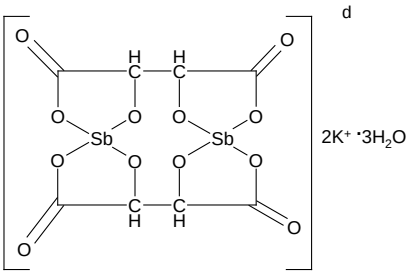
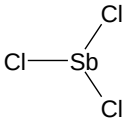
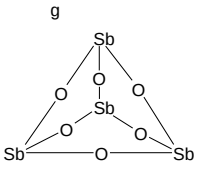
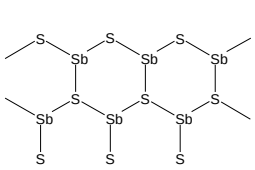
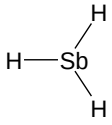
Characteristic	Information	
Chemical name	Ammonium potassium tartrate	Antimony trichloride
Synonym(s)	Antimonial potassium tartrate; potassium antimonial tartrate; tartox; tartrated antimony; potassium antimony tartrate; tartar emetic	Antimonous chloride; antimony butter; antimony(III) chloride; trichlorostibine; chloride antimony
Registered trade name(s)	No data	No data
Chemical formula	$C_8H_4K_2O_{12}Sb_2 \cdot 3H_2O$[d]	Cl_3Sb
Chemical structure		
CAS Registry Number	28300-74-5	10025-91-9

Table 4-1. Chemical Identity of Antimony and Compounds[a]

Characteristic	Information		
Chemical name	Antimony trioxide	Antimony trisulfide	Stibine
Synonym(s)	Antimonious oxide; antimony oxide; diantimony trioxide[d]; flowers of antimony[d]; antimony sesquioxide[e]; senmarmontite; valentinite; antimony white; antimony peroxide; timothox; exitelite	Antimonous sulfide; antimony glance; antimony orange; 130antimony crimson; antimony sesquisulfide; antimony sulfide; antimony vermilion; stibite; antimony needles	Antimony hydride; antimony trihydride; hydrogen antimonide
Registered trade name(s)	Hd[f]; LP[f]; KR[f]; White Star[f]; White Star M[f]; KR-LTS[f]; Thermoguard S[f]; Thermoguard L[f]; H Grade[f]; L Grade[f]; Fire Shield L[f]; Montana Brand[f]	No data	No data
Chemical formula	O_3Sb_2	S_3Sb_2	H_3Sb
Chemical structure	 [g]	 [g]	
CAS Registry Numer	1309-64-4	1345-04-6	7803-52-3

[a]All information obtained from HSDB (2005a, 2005b, 2009a, 2009b, 2013, 2014) except where noted.
[b]Weast 1988.
[c]RTECS 2015.
[d]Windholz 1983.
[e]Freedman et al. 1978.
[f]Avento and Touval 1980.
[g]Cotton and Wilkinson 1966.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of antimony and selected antimony compounds are given in Table 4-2. Antimony metal is stable under ordinary conditions. Antimony is a poor conductor of heat and electricity (Li 2011). Antimony forms complex ions with organic and inorganic acids. Stable complexes, such as $Sb_2S_4^{2-}$, may form when antimony is in the presence of sulfur (Bodek et al. 1988).

Stibine (SbH_3) is a gaseous antimony compound in which antimony is in the -3 valence state. Stibine is formed by the action of acids on metal antimonides or antimony alloys by the reduction of antimony compounds, or by the electrolysis of acidic or basic solutions where antimony is present in the cathode. There is a danger of stibine being liberated from overcharged lead storage batteries in which antimony is alloyed into the lead. Stibine slowly decomposes into metallic antimony and hydrogen. It is readily, and sometimes violently, oxidized by air to form antimony trioxide and water (Freedman et al. 1978).

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information		
Chemical name	Antimony	Antimony pentasulfide	Antimony pentoxide
Molecular weight	121.75	403.80	323.5 (anhydrous)
Color	Silvery white	Yellow	Yellow
Physical state	Solid	Solid	Solid
Valence state	0	+5	+5
Melting point (°C)	630.5	75 (decomposes)	380 (decomposes)[f]
Boiling point (°C)	1,750; 1,325[b]; 1,635[c]	No data	No data
Density (g/cm^3) at 20°C	6.684 (at 25°C); 6.688[b]	4.12	3.78
Odor	No data	Odorless[c]	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water at 20°C	Insoluble	Insoluble	Very slightly soluble
Organic solvents	No data	Insoluble	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure (mmHg) at 20°C	1 (at 886°C)[d]	No data	No data
Henry's law constant at 25°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]	None[e]
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information	
Chemical name	Antimony potassium tartrate	Antimony trichloride
Molecular weight	333.93	228.11
Color	Colorless	Colorless
Physical state	Solid	Solid
Valence state	+3	+3
Melting point (°C)	100 (-½ mole H_2O)	73.4
Boiling point (°C)	No data	283, 222.6[g]
Density (g/cm^3) at 20°C	2.6	3.140 (at 25°C)
Odor	Odorless[g]	Sharp, unpleasant
Odor threshold:		
Water	No data	No data
Air	No data	No data
Taste	Sweetish, metallic[c]	No data
Taste threshold	No data	No data
Solubility		
Water at 20°C	83 g/L (cold)	6,016 g/L (at 0°C)
Organic solvents	Insoluble in alcohol; soluble in glycerine	Soluble in ABS alcohol, tartaric acid, methylene chloride, benzene, acetone
Partition coefficients		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure (mmHg) at 20°C	No data	1 (at 49.2°C, sublimes)
Henry's law constant at 25°C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information		
Chemical name	Antimony trioxide	Antimony trisulfide	Stibine
Molecular weight	291.50	339.69	124.77
Color	White (senarmontite); colorless (valentinite)	Black (stibinite); yellow-red (amorphous)	Colorless[g]
Physical state	Solid	Solid	Gas
Valence state	+3	+3	-3
Melting point (°C)	656	550	-88
Boiling point (°C)	1,550 (sublimes); 1,425[g]	1,150	-17[g]
Density (g/cm^3) at 20°C	5.2 (senarmontite); 5.67 (valentinite)	4.64 (stibinite); 4.12 (amorphous solid)	2.204 (at -17°C)
Odor	Odorless	No data	Disagreeable, like hydrogen sulfide[g]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility			
Water at 20°C	Very slightly soluble	1.75 mg/L (at 18°C)	4.1 g/L (at 0°C)
Organic solvents	Soluble in tartaric acid, acetic acid, hydrochloric acid	Soluble in alcohol; insoluble in acetic acid	Soluble in carbon disulfide, ethanol[g]
Partition coefficients			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure (mmHg) at 20°C	1 (at 574°C)[d]	No data	No data
Henry's law constant at 25°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]	1 ppm stibine = 5.1 mg/m^3
Explosive limits	No data	No data	No data

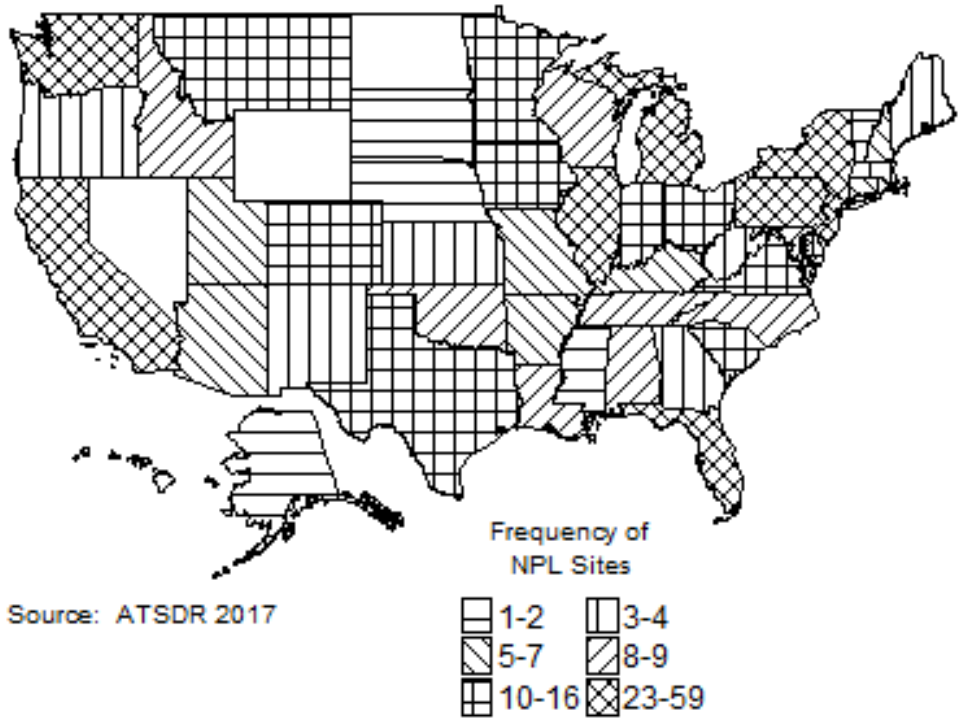
[a]All information obtained from Weast (1988) except where noted.
[b]Herbst et al. 1985.
[c]Windholz 1983.
[d]HSDB 2013.
[e]Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.
[f]Lewis 2012.
[g]Freedman et al. 1978.

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Antimony or antimony compounds have been identified in at least 563 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which antimony has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 556 are located within the United States, 2 are located in the Virgin Islands, 1 is located in Guam, and 4 are located in Puerto Rico (not shown)

Figure 5-1. Number of NPL Sites with Antimony or Antimony Compounds Contamination



- Antimony is a natural constituent of soil and is transported into streams and waterways from natural weathering of soil, as well as from anthropogenic sources (EPA 1979; Mok and Wai 1990). Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 µg/g (ppm), but these levels vary by location (Telford et al. 2008). Studies indicate that antimony is retained in the soil through adsorption and can sorb onto clay minerals, oxides, and hydroxides in the soil and aquatic sediment (Wilson et al. 2010). The general population is exposed to low levels of antimony in ambient air and food. Individuals can be exposed to antimony in polyethylene terephthalate (PET) water bottles (reviewed in Belzile et al. 2011) or from products containing

antimony flame retardants. Occupationally exposed workers will have the highest levels of exposure to antimony (Quiroz et al. 2011; Smith et al. 1995).

- Background levels of antimony in ambient air are typically <20 ng/m^3. However, levels of antimony in ambient air can be >1,000 ng/m^3 near plants that convert antimony ores into metal or manufacture substances such as antimony trioxide (Ragaini et al. 1977).

- Background levels of antimony in groundwater in the United States from 1992 to 2003 were low, with median concentrations of <1 μg/L (USGS 2011). Anthropogenic activity such as mining activities, and coal and municipal waste combustion can result in increases in antimony levels in ambient water (Jablonska-Czapla et al. 2014). Most dissolved antimony in natural waters under aerobic conditions is present in the pentavalent oxidation state as antimonate species ($Sb(OH)_6^-$). Anthropogenic emissions commonly contain antimony in the trivalent oxidation state (e.g., antimony trioxide); however, it is unclear how quickly antimonite oxidizes to antimonate under natural conditions. Under anoxic reducing conditions, trivalent species such as $Sb(OH_3)$, $Sb(OH_4)^-$, and $Sb_2S_4^-$ are the most thermodynamically stable forms of antimony.

- Antimony can be reduced and methylated by microorganisms in anaerobic sediment, releasing volatile methylated antimony compounds into the water. Multiple microorganisms have been found to methylate antimony in the soil and water and some anoxic or poorly oxygenated environments (Bentley and Chasteen 2002).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Tables 5-1 and 5-2 list the number of facilities in each state that have produced, imported, processed, or used antimony and antimony compounds, respectively, according to reports made to the EPA under requirements of Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 and subsequently published in the Toxic Chemical Release Inventory (TRI17 2018). Only certain types of facilities were required to report; therefore, this is not an exhaustive list. The number of individual facilities and the amount produced on site varied in each state.

Table 5-1. Facilities that Produce, Process, or Use Antimony

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	2	10,000	999,999	1, 5, 7, 8
AR	1	10,000	99,999	7, 8
CA	4	0	99,999	9, 12, 14
CT	1	1,000	9,999	7
FL	1	100,000	999,999	1, 5

Table 5-1. Facilities that Produce, Process, or Use Antimony

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
IA	2	100	99,999	8
ID	3	1,000	999,999	8, 9, 12
IL	1	10,000	99,999	8, 11
IN	3	1,000	99,999	1, 5, 7, 8, 9
KS	2	10,000	99,999	1, 4, 7, 8
KY	2	10,000	99,999	2, 3, 4, 6, 7, 8, 9
MI	2	100	99,999	7
MN	2	10,000	999,999	7, 8, 14
MO	4	1,000	99,999	1, 6, 8, 9, 12, 13
MS	2	10,000	99,999	8
MT	1	100,000	999,999	1, 2, 3, 4, 5, 7
NC	4	1,000	99,999	7, 8, 14
NE	2	1,000	99,999	7, 8
NJ	2	1,000	999,999	2, 4, 9, 11
NV	2	1,000	99,999	8, 12
NY	4	0	9,999	8, 14
OH	11	100	999,999	1, 2, 3, 7, 8, 9, 10, 11
PA	8	1,000	999,999	2, 3, 4, 7, 8, 9, 10
SC	1	10,000	99,999	1, 5, 7, 14
TN	5	0	99,999	1, 4, 7, 8, 12
TX	2	10,000	99,999	8, 9
VA	1	10,000	99,999	7
WA	2	1,000	99,999	7, 8, 11
WI	1	1,000	9,999	8

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI17 2018 (Data are from 2017)

Table 5-2. Facilities that Produce, Process, or Use Antimony Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10,000	99,999	1, 5, 12, 13, 14
AL	6	1,000	99,999	7, 8, 10, 11
AR	2	1,000	99,999	1, 5, 8, 9, 12
AZ	3	10,000	999,999	1, 2, 5, 8, 13, 14
CA	15	100	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 12
CO	2	100,000	999,999	1, 2, 3, 4, 6, 12, 13, 14
CT	4	10,000	99,999	7, 8
DE	2	10,000	99,999	1, 2, 3, 4, 7, 8, 13, 14
FL	2	10,000	999,999	2, 3, 7, 8
GA	22	1,000	999,999	1, 2, 3, 5, 6, 7, 8, 11, 14
IA	1	10,000	99,999	7
ID	4	1,000	99,999	1, 5, 7, 8, 12, 13, 14
IL	16	1,000	999,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13
IN	29	100	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
KS	5	1,000	999,999	1, 3, 6, 7, 8
KY	17	100	999,999	1, 2, 3, 4, 6, 7, 8, 10, 11, 13
LA	9	0	99,999	1, 5, 7, 10, 11, 12, 13, 14
MA	17	1,000	999,999	1, 2, 3, 4, 6, 7, 8, 9
MD	1	0	0	0
MI	10	1,000	99,999	1, 2, 3, 4, 5, 7, 8, 9, 14
MN	9	1,000	999,999	7, 8, 9
MO	8	1,000	9,999,999	1, 2, 3, 4, 7, 8
MS	11	1,000	9,999,999	6, 7, 8, 12
MT	2	100,000	999,999	1, 5, 12, 14
NC	22	0	99,999	2, 3, 6, 7, 8, 9, 10, 14
ND	1	100,000	999,999	1, 5, 12, 13, 14
NE	4	1,000	99,999	6, 7, 8, 12
NH	2	10,000	99,999	7, 8
NJ	10	1,000	999,999	2, 5, 7, 8, 10, 11
NV	7	1,000	9,999,999	1, 2, 5, 7, 12, 13, 14
NY	3	1,000	99,999	7, 8, 14
OH	44	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
OK	1	1,000	9,999	12
OR	3	10,000	99,999	2, 3, 4, 7, 8
PA	29	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
PR	1	10,000	99,999	6, 10
RI	4	1,000	99,999	7, 8, 12
SC	23	0	999,999	1, 2, 3, 6, 7, 8, 10, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Antimony Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	21	100	9,999,999	1, 2, 3, 5, 6, 7, 8, 10, 13, 14
TX	41	100	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	5	10,000	49,999,999	1, 3, 4, 5, 7, 8, 9, 12, 13
VA	7	1,000	999,999	6, 7, 8
VT	2	1,000	99,999	7, 8
WA	1	0	0	0
WI	12	100	999,999	1, 3, 5, 7, 8, 11, 13, 14
WV	5	1,000	99,999	1, 5, 7, 8
WY	1	100,000	999,999	1, 3, 4, 9, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI17 2018 (Data are from 2017)

Fifteen countries mine antimony. The world total mine production was 118,000 metric tons in 2000 (USGS 2004). The majority, 85% of the world total, of antimony is mined in China. Between 1977 and 1984, the amount of antimony mined in the United States ranged from 311 to 760 metric tons (Llewellyn 1989; Plunkert 1982). The United States no longer mines antimony. The last domestic mine in the United States closed in 2001. According to the U.S. Bureau of Mines, six companies produced primary antimony metal and metal oxide products in the United States in 1992. These six companies were ASARCO Incorporated, Omaha, Nebraska; Amspec Chemical Corp., Gloucester City, New Jersey; Welcome29 America, Laredo, Texas; Laurel Industries Inc., La Porte, Texas; Sunshine Mining Co., Kellogg, Idaho; and U.S. Antimony Corp, Thompson Falls, Montana (HSDB 2005a).

In 1992, the total U.S. primary antimony consumption was 12,221 metric tons, of which 3,297 metric tons were for metal products, 2,103 metric tons for nonmetal products, and 6,821 metric tons for flame retardants (USGS 2004). Most of the primary antimony generated in the United States was generated as antimony trioxide. Antimony trioxide is produced by oxidizing antimony sulfide ore or antimony metal in air at 600–800°C (Avento and Touval 1980). In 1987 and 1988, 18,758, and 18,226 metric tons of the

oxide were produced, respectively (U.S. Bureau of Mines 1989). Consumption trends have generally paralleled those of production.

Antimony is also produced as a byproduct of smelting primary lead ores. Primary smelter outputs were 19,675 metric tons in 1992. Almost as much antimony is produced from scrap as from ore. Antimony produced from secondary sources is primarily derived from "old scrap," generally consisting of lead battery plates, type metal, and bearing metal. "New scrap," which is derived from drosses and scrap generated during fabrication, constituted 6% of the secondary antimony in 1992 (HSDB 2005a; Llewellyn 1989). Secondary antimony is chiefly consumed as antimonial lead; a small percentage goes into the production of other lead- and tin-based alloys. Secondary antimony production was 17,736 metric tons in 1992, with 1,043 metric tons originating from new scrap and 16,693 metric tons from old scrap (HSDB 2005a; Llewellyn 1989; Plunkert 1982).

The method of treating antimony ore after mining depends on the type of ore and its antimony content. High-grade (45–60%) sulfide ore that is free from lead and arsenic can be extracted by melting using a technique known as liquation. In this process, the ore is heated to 550–660°C in a crucible or reverberatory furnace in a reducing atmosphere. Also, high-grade sulfide ores can be reduced to the metal by a technique in which the ore is heated with iron scrap, known as iron precipitation. The iron replaces the antimony, forming iron sulfide. Another antimony ore treatment technique takes high-grade oxide ores and reduces them with charcoal in a reverberatory furnace. An alkaline flux is used to reduce volatilization losses; loss of antimony due to volatilization can be as high as 12–20%. The method of choice for low-grade (<20%) sulfide ores is volatilizing roasting. In this process, the ore is heated to about 500°C in a controlled amount of oxygen, so that the antimony trioxide formed is volatilized and then recondensed. Intermediate-grade sulfide or oxide ores are generally handled by smelting (Carapella 1978; Herbst et al. 1985). The impure metal may be refined by pyrometallurgical techniques or electrolysis.

5.2.2 Import/Export

China is the largest exporter of antimony to the United States, most of which is imported as antimony metal. In 2014, total U.S. imports were 365 metric tons for ore and concentrate, 6,210 metric tons for metal, alloys, waste, and scraps, and 17,600 metric tons for antimony oxide. Total U.S. imports were 24,200 metric tons in 2014 and 24,700 metric tons in 2013 (USGS 2015).

The last domestic antimony producing mine in the United States closed in 2001. In 1988, the United States exported 624 metric tons of antimony metal, alloys, and scrap and 1,227 metric tons of antimony oxide (U.S. Bureau of Mines 1989). Canada was the largest recipient of these exports. The United States also exported 942 metric tons of antimony metal, alloy, waste, and scrap in 1992 (HSDB 2005a).

5.2.3 Use

Pure antimony is a brittle metal and is restricted in its use due to its poor mechanical properties (Grund et al. 2012; HSDB 2005a). As an alloy, it is mixed with other metals to increase their hardness, mechanical strength, corrosion resistance, and electrochemical stability or to decrease their coefficient of friction. Some antimony alloys expand slightly upon cooling, a valuable property for use in type metal and other castings (Carapella 1978). Antimonial lead is used in small arms ammunition, cable sheathing and lead pipe, and the storage-battery grids, grid plates, straps, and terminals of lead-acid batteries (Grund et al. 2012).

The application of antimony in lead-acid batteries has decreased, and most of the use of antimony in the batteries is in recycling. Historically, antimony improves fluidity and electrical stability, and increases the fatigue strength and creep resistance of the lead in the batteries (Carapella 1978). Alloys of tin and antimony are utilized in electrical equipment, such as the end and side seams of cans, car radiators, and plumbing. Alloys of tin, copper, and antimony are utilized to produce Britannia metal and pewter. Metal products utilize 20% of primary antimony produced (Grund et al. 2012), and 50% of primary antimony is used in plastics to impart flame retardancy. Antimony trioxide is utilized as a flame retardant when combined with a halogen (van Velzen et al. 1998). Antimony is used in the manufacture of chromate pigments, as an opacifer for ceramic glaze, as a gas bubble and color remover in lead crystal glass and glass for television tubes, and as a polymerization catalyst to manufacture polyester fibers (Grund et al. 2012).

Antimony compounds have also been used for the treatment of parasitic diseases such as leishmaniasis. Other antimony salts are used in certain pesticides, ammunition primers, flares, tracer shells, and fireworks, and in the manufacture of disk-brake pads and cutting disks (Grund et al. 2012).

5.2.4 Disposal

Much of the antimony used in antimonial lead is recycled. This is evident from the large amount of secondary antimony production. Most antimonial lead comes from auto batteries. Little information concerning the disposal of antimony and its compounds has been found in the literature. Wastes from mining and smelting are generally disposed of in landfills. This is evident from the amounts of releases to land from companies that produce antimony and its compounds (Section 5.3.1). In addition, many companies transfer their antimony waste to publicly-owned treatment works or to off-site facilities for disposal. Plastics and articles of clothing that contain small amounts of antimony oxide flame retardants will generally be placed in landfills or undergo incineration along with normal industrial or municipal trash.

Antimony and its compounds have been designated as priority pollutants by EPA (1988). As such, persons who generate, transport, treat, store, or dispose of antimony-containing material must comply with regulations of the federal Resource Conservation and Recovery Act (RCRA). No limitations on the disposal of antimony ore from mines and mills have been promulgated in the Code of Federal Regulations (EPA 1988).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 6,779 pounds (~3.07 metric tons) of antimony to the atmosphere from 77 domestic manufacturing and processing facilities in 2017, accounted for about 0.79% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-3. Estimated releases of 16,901 pounds (~7.66 metric tons) of antimony compounds to the atmosphere from 441 domestic manufacturing and processing facilities in 2017, accounted for about 0.11% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-4.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Antimony[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	2	108	83	0	513,764	2	513,931	26	513,957
AR	1	54	166	0	5,297	No data	220	5,297	5,517
CA	4	1	No data	0	90,051	7	89,573	486	90,059
FL	1	9	1,961	0	No data	9,549	9	11,510	11,519
IA	2	2	1	0	12,331	No data	12,334	1	12,334
ID	3	3	0	0	No data	No data	3	0	3
IL	1	257	255	0	15,001	14,105	262	29,356	29,618
IN	3	No data	No data	0	0	No data	0	No data	0
KS	2	34	1	0	No data	No data	34	1	35
KY	2	2	0	0	No data	0	2	0	2
MI	2	0	0	0	9,722	No data	1	9,722	9,723
MN	2	3	446	0	81,381	No data	3	81,826	81,829
MO	4	6	42	0	1,463	3,781	1,452	3,840	5,292
MS	2	1	12	0	No data	246	1	258	259
MT	1	5,346	No data	0	No data	No data	5,346	No data	5,346
NC	4	21	No data	0	3,773	No data	3,114	680	3,794
NE	2	59	5	0	No data	31	59	36	95
NJ	2	No data	No data	0	No data	No data	No data	No data	No data
NV	2	1	No data	0	10,035	No data	10,031	5	10,036
NY	4	35	942	0	31	2,035	40	3,003	3,043
OH	11	62	No data	0	634	5,296	62	5,930	5,992
PA	8	68	324	0	15	4,052	78	4,381	4,460

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Antimony[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
SC	1	2	4	0	26,739	No data	2	26,743	26,745
TN	5	505	255	0	1,419	35,773	1,929	36,023	37,952
TX	2	2	No data	0	No data	No data	2	No data	2
VA	1	181	No data	0	No data	384	181	384	565
WA	2	20	No data	0	211	No data	20	211	231
WI	1	0	No data	0	No data	No data	0	No data	0
Total	77	6,779	4,497	0	771,868	75,261	638,686	219,720	858,406

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI17 2018 (Data are from 2017)

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Antimony Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	No data	20	No data	8,500	No data	8,520	No data	8,520
AL	6	10	5	No data	6,327	1,034	15	7,361	7,376
AR	2	1	5	No data	43,198	No data	43,184	20	43,204
AZ	3	548	10	No data	468,233	No data	468,784	7	468,791
CA	14	21	597	No data	321,857	7,261	405	329,331	329,736
CO	2	12	No data	No data	2,635	No data	12	2,635	2,647

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Antimony Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
CT	4	10	173	No data	4,443	27,255	10	31,871	31,881
DE	2	0	No data	No data	No data	23	0	23	24
FL	2	No data	No data	No data	1,534	No data	No data	1,534	1,534
GA	22	562	161	No data	33,095	18,005	574	51,249	51,823
IA	1	1	No data	No data	No data	No data	1	No data	1
ID	4	462	803	No data	131,730	496	132,255	1,236	133,491
IL	16	255	439	No data	39,741	4,369	36,024	8,779	44,803
IN	29	2,084	7,410	No data	1,110,798	73,297	77,170	1,116,419	1,193,589
KS	5	371	0	No data	5,326	476	371	5,802	6,173
KY	17	1,434	151	No data	33,173	5,844	7,648	32,955	40,603
LA	9	561	3,565	No data	27	558	4,126	585	4,711
MA	17	No data	No data	No data	No data	No data	No data	No data	No data
MD	1	681	585	No data	6,888	37,928	684	45,398	46,082
MI	10	290	84	No data	6,369	269	290	6,722	7,012
MN	9	69	12	No data	3,789	2,124	69	5,925	5,994
MO	9	5	246	No data	201,000	65	191,639	9,677	201,316
MS	11	2,067	112	No data	2,664	38,965	2,068	41,740	43,808
MT	2	140	No data	No data	9,660	4	9,800	4	9,804
NC	19	115	149	No data	13,295	6,851	514	19,896	20,410
ND	1	1,201	No data	No data	77,300	No data	78,501	No data	78,501
NE	4	10	5	No data	39,309	338	28,061	11,601	39,662
NH	2	No data	No data	No data	1,286	No data	No data	1,286	1,286
NJ	10	120	15	No data	3,429	10,328	125	13,767	13,892
NM	7	28	No data	No data	96,868	No data	28	96,868	96,896
NV	3	67	72	No data	10,664,735	No data	10,664,045	829	10,664,874
OH	43	792	15,172	526	40,611	11,210	1,071	66,715	67,785
OK	1	No data	No data	No data	20,627	No data	20,627	No data	20,627
OR	3	29	No data	No data	No data	1,216	29	1,216	1,245
PA	29	205	1,636	No data	94,723	47,621	6,893	137,292	144,185
PR	1	10	No data	No data	65,993	No data	10	65,993	66,003
RI	4	3	2	No data	5,817	5,502	3	11,321	11,324
SC	23	498	4,754	1	8,944	2,370	2,622	13,944	16,566
TN	20	371	1,191	No data	65,270	434	38,927	28,339	67,265
TX	41	1,640	1,173	19,412	430,283	90,242	365,172	158,165	523,337
UT	5	161	1,000	No data	410,695	14,112	194,388	231,579	425,967

Table 5-4. Releases to the Environment from Facilities that Produce, Process, or Use Antimony Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
VA	7	111	274	No data	4,162	133	136	4,544	4,680
VT	2	No data	No data	No data	No data	No data	No data	No data	No data
WA	1	No data	No data	No data	No data	No data	No data	No data	No data
WI	11	1,850	9	No data	80,561	6,703	1,853	87,270	89,124
WV	5	62	No data	No data	2,238	No data	623	1,677	2,300
WY	1	46	No data	No data	791	No data	837	No data	837
Total	441	16,901	39,831	19,938	14,567,922	415,035	12,388,114	2,651,577	15,039,691

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI17 2018 (Data are from 2017)

Section 112 of the Clean Air Act (CAA) lists antimony as one of 188 hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage (EPA 2000). EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on-road and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Using composite data from the NTI database from 1990 to 1993, it was estimated that the annual emissions of antimony in the United States

were approximately 103 tons per year during that time frame (EPA 2000). Data downloaded from the 2011 NEI (see Table 5-5) indicated that the total emission of antimony was approximately 5,210,763 pounds, with the biggest contribution arising from electric generation by coal (EPA 2016a).

Table 5-5. 2011 National Emission Inventory (NEI) Total National Emissions

Name	Annual emissions (lb)
Bulk gasoline terminals	2.5134
Commercial cooking	264.183
Dust, construction dust	5.26327
Fires, agricultural field burning	330.6032
Fuel combustion, commercial/institutional, biomass	67.40831
Fuel combustion, commercial/institutional, coal	40.24683
Fuel combustion, commercial/institutional, natural gas	0.09
Fuel combustion, commercial/institutional, oil	143.801
Fuel combustion, commercial/institutional, other	1.411491
Fuel combustion, electric generation, biomass	188.6612
Fuel combustion, electric generation, biomass coal	13,020.77
Fuel combustion, electric generation, biomass natural gas	78.23796
Fuel combustion, electric generation, biomass oil	5,978.314
Fuel combustion, electric generation, biomass other	25.92661
Fuel combustion, industrial boilers, internal combustion engines, biomass	2,206.582
Fuel combustion, industrial boilers, internal combustion engines, coal	2,513.459
Fuel combustion, industrial boilers, internal combustion engines, natural gas	1,682.659
Fuel combustion, industrial boilers, internal combustion engines, oil	311.0068
Fuel combustion, industrial boilers, internal combustion engines, other	801.3158
Fuel combustion, residential, natural gas	0
Fuel combustion, residential, oil	0.00051
Fuel combustion, residential, other	0.647524
Industrial processes, cement manufacturing	78.64444
Industrial processes, chemical manufacturing	1,502.073
Industrial processes, ferrous metals	1,071.269
Industrial processes, mining	94.03349
Industrial processes, not elsewhere classified	25,172.5
Industrial processes, nonferrous metals	11,997.31
Industrial processes, oil and gas production	220.7644
Industrial processes, petroleum refineries	2,073.725
Industrial processes, pulp and paper	1,857.656
Industrial processes, storage and transfer	597.7857
Miscellaneous non-industrial, not elsewhere classified	20.64527
Mobile, commercial marine vessels	69.72685
Mobile, locomotives	314.1618

Table 5-5. 2011 National Emission Inventory (NEI) Total National Emissions

Name	Annual emissions (lb)
Solvent, degreasing	416.547
Solvent, graphic arts	19.95
Solvent, industrial surface coating and solvent use	6,836.025
Waste disposal	407.8158
Total	5,210,763

Source: EPA 2016a

Releases of antimony to the atmosphere result from natural and anthropogenic sources. Total emissions from both sources were reported to be 6,100 tons/year in the 1980s; anthropogenic sources such as coal combustion, smelting, and refining were the major sources (Belzile et al. 2011). It was also estimated that 41% of antimony emissions to the air were from natural sources in the 1980s. The natural sources and their median percentage contribution were: wind-borne soil particles, 32.5%; volcanos, 29.6%; sea salt spray, 23.3%; forest fires, 9.2%; and biogenic sources, 12.1% (Nriagu 1989).

Total mid-1990 atmospheric emissions of antimony were reported to be 1,561 tonnes/year total from anthropogenic sources. Emissions from the combustion of fuels, lead production, zinc production, copper production, nonferrous production, pig iron and steel production, municipal waste, and sewage sludge were found to be 319, 134, 95, 547, 7, 235, 34, and 730 tonnes, respectively (Pacyna and Pacyna 2001).

Atmospheric particulate matter was found to be enriched with antimony in Japan; brake abrasion dust from automobiles and waste fly ash were found to be the predominant sources of antimony emissions. Emissions were estimated to be 21 tonnes/year from brake pads (Iijima et al. 2009). Antimony levels in high-density traffic areas are likely due to abrasion of tires, brake lining, and other automotive components that use of antimony alloys (Belzile et al. 2011). In Gottingen, Germany, 176 kg/year of antimony is emitted from brakes, tires, street surfaces, and vehicle exhaust (WHO 2003).

Increased emissions from fly ash were also reported in Japan. Fly ash is produced in waste incineration (Iijima et al. 2009). Antimony concentrations in fly ash were reported to be 4.7 µg/g total in Japan, 1–3.9 µg/g in various countries, and 1.99 µg/g total in Spain (Smichowski 2008).

5.3.2 Water

Estimated releases of 4,497 pounds (~2.04 metric tons) of antimony to surface water from 77 domestic manufacturing and processing facilities in 2017, accounted for about 0.52% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs). These releases are summarized in Table 5-3. Estimated releases of 39,831 pounds (~18.07 metric tons) of antimony compounds to surface water from 441 domestic manufacturing and processing facilities in 2017, accounted for about 0.26% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-4.

Antimony is a natural constituent of soil and is transported into streams and waterways in runoff either due to natural weathering or disturbed soil (Cole et al. 1984).

Antimony is also found in water due to contamination from mining and smelter, shooting ranges, and road sides that contain dust from brake pads and tires.

5.3.3 Soil

Estimated releases of 771,868 pounds (~350.11 metric tons) of antimony to soil from 77 domestic manufacturing and processing facilities in 2017, accounted for about 89.92% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-3. Estimated releases of 14,567,922 pounds (~6,607.89 metric tons) of antimony compounds to soil from 441 domestic manufacturing and processing facilities in 2017, accounted for about 96.86% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). An additional 19,938 pounds (~9.04 metric tons), accounted for about 0.13% of the total environmental emissions were released via underground injection (TRI17 2018). These releases are summarized in Table 5-4.

Antimony is a natural constituent of soil and is produced from the weathering of soil parent materials (Wilson et al. 2010). Contamination of the soil leads to increased concentrations of antimony. Most of the antimony released to the environment is released to land. The industries that release the largest amount of antimony are smelters that produce antimony and antimony trioxide. Much of this release is slag, which is the residue from smelting operations. Other releases to land include sludge from publicly

owned treatment works (POTWs) and municipal refuse (Eckel and Langley 1988). Munitions may also be a source of antimony soil contamination (Hockmann et al. 2014; Mariussen et al. 2017).

Antimony was reported to be in 166 of the 1,397 soil samples at the Lawrence Berkeley National Laboratory. The samples were obtained from soil boring sites from the construction of 71 groundwater monitoring wells. A 12% occurrence of antimony was reported, and levels found in the sample site (0.7–22 mg/kg) exceeded the background levels of antimony normally found in the soil (DOE 2009a).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

The oxidized form of antimony, Sb(V), is expected to be the more stable form in the environment; however, Sb(III) is formed under certain environmental conditions (Mitsunobu et al. 2006). Similarly, inorganic species are expected to be more present than organic species of antimony in most environmental systems (Wilson et al. 2010).

Sb(V) corresponds to the octahedral antimonite ion, $Sb(OH)_6^-$, while Sb(III) corresponds to the uncharged antimonous acid, $Sb(OH)_3$ in antimony water systems. In the soil, antimony oxidation state and environmental reactions are largely dependent on the pH, redox conditions, and concentrations of co-occurring reduction agents and oxidants in the system (Wilson et al. 2010).

Antimony can be retained in the soil primarily through adsorption. Antimony can sorb to clay minerals, or to oxides and hydroxides in the soil. Sb(III) sorbs more strongly to manganese (III) oxyhydroxide (MnOOH) than to aluminum hydroxide ($Al(OH)_3$) or iron(III) oxide-hydroxide (FeOOH) (Wilson et al. 2010). Antimony K_d values ranged from 1 to 2,065 L/kg in a sorption study investigating plant uptake of antimony (Nakamaru and Sekine 2008).

Antimony behavior in soil-water systems was found to be dependent on redox conditions in a study evaluating soil collected at different depths at the Ichinokawa mine pit in Ehime, Japan. Decreased antimony concentrations were observed in the soil as the water saturation increased. Sb(V) was found to be stable under reducing conditions. Antimony was found to have a positive correlation with iron and manganese in the soil (Mitsunobu et al. 2006).

Sb(III) was found to bind more strongly to solids than Sb(V) in a study evaluating antimony solubility in soil from shooting ranges. Sorption of antimony was highly dependent on pH. At pH levels <7, Sb(V) was found to be almost completely sorbed. At pH levels of at least 10, Sb(III) was found to be sorbed. The total release of antimony was found to be much higher than the releases from nickel, copper, bismuth, thallium, and mercury in the soil at the seven Swiss shooting ranges (Johnson et al. 2005).

Miravet et al. (2006) examined the mobility of antimony from coal fly ash. Fly ash, from coal fired power plants, contains a mixture of chemicals that may be distributed to soils, freshwater, seawater, or groundwater. Some portions of fly ash are not extractable or are unavailable under environmental conditions; however, the leachable portion of fly ash has the potential to accumulate in organisms. Antimony was found to leach out of fly ash solution at pH 1–12. Sb(V) was the major antimony species in the leachate. Antimony was partially soluble at pH 5, and more soluble at acidic pH values.

Leaching experiments performed with river sediment samples from a mining district in Idaho also indicated that Sb(V) was the major species released during leaching (Mok and Wai 1990). The fraction of antimony leached from sediment with deionized water after 10 days was highly correlated with the free iron and manganese oxide content of the sediment (correlation coefficients of 0.90 and 0.75, respectively). Experiments on the pH dependence of leaching showed marked differences between trivalent and pentavalent antimony (Mok and Wai 1990). The release of trivalent antimony from the sediment increased at low pH; in contrast, the release of pentavalent antimony from sediment increased sharply at high pH (pH 11.4). At pH 4.3, the concentrations of tri- and pentavalent antimony were comparable. Antimony does not appear to bioconcentrate appreciably in fish and aquatic organisms. No detectable bioconcentration occurred during a 28-day test in bluegills (EPA 1980). Only low levels of antimony have been reported in fish and aquatic organisms collected off the coast of Africa, Australia, and the Danube River in Austria (EPA 1979; Maher 1986). Bioconcentration factors for antimony ranged from 0.15 to 390 (Acquire 1989; EPA 1979).

Antimony sorption was studied in relation to its plant uptake. Antimony K_d values ranged from 1 to 2,065 L/kg. The K_d values were significantly decreased with increasing phosphate concentrations, indicating that the addition of phosphate fertilizer may increase the potential for antimony uptake in plants. No difference in antimony sorption to soil occurred when sulfates were added to the soil in this study (Nakamaru and Sekine 2008).

Antimony can be taken up by plants through the roots and via surface deposition from aerosols. Surface deposition is the major pathway for soil-to-plant transfer of antimony in field conditions (Tschan et al. 2009).

The *Viola* species were found to accumulate antimony in their roots, stems, leaves, flowers, and seeds. Mean antimony concentrations in *Viola allcharensis* were 0.46 mg/kg in the root, 0.34 mg/kg in the stem, 0.46 mg/kg in the leaf, 0.25 mg/kg in the flower, and 0.40 mg/kg in the seed. Mean antimony concentrations for the root, stem, leaves, flowers, and seeds of *Viola arsenica* were reported as 1.06, 0.25, 0.72, 0.47, and 0.91 mg/kg, respectively. Mean antimony concentrations for *Viola macedonica* were 0.25 mg/kg for each root, stem, leaves, and flowers (Baceva et al. 2014).

Certain plants may be used in phytoremediation because they are able to accumulate metals in their tissues and have a high tolerance for those metals in contaminated soils. In the Sao Domingos copper mine, several plant species were found to accumulate antimony in their systems. Concentrations of antimony in the mine tailings ranged from 203 to 2,513 mg/kg. Concentrations in plant species were 6.67 mg/kg for *Erica andevalensis*, 4.09 mg/kg for *Erica australis*, 3.59 mg/kg for *Corrigiola telephypholia*, 2.8 mg/kg for *Echium* plantagium, 2.02 mg/kg for *Eritrae pulcheria*, and 0.60 mg/kg for *Daphne gnidium* and other plants (Anawar et al. 2011).

Root tissues of Maize (*Zea mays*) contained 0.35, 2.5, 3.98, 22.01, and 26.5–68.42 mg/kg of antimony, when exposed to 10, 50, 100, 500 and 1,000 mg/kg of antinomy, respectively. Concentrations of antimony at 10, 50, 100, 500, and 1,000 mg/kg corresponded to 0.82, 6.32, 13.76, 45.1, and 68.42 mg/kg in the shoot tissues. Higher concentrations of antimony resulted in higher antimony accumulation in the plants in this study (Pan et al. 2010).

In a similar study, antimony uptake was measured in maize (*Z. mays*) and sunflowers (*Helianthus annuus*). No significant differences in uptake between the two plant species were observed. The bioaccumulation coefficient was reported as 0.93 for maize and 1.33 for sunflower (Tschan et al. 2008).

The mechanism of Baker yeast cell (*Saccharomyces cerevisiae*) antimony biosorption has also been investigated. Sb(III) was removed from contaminated aqueous samples and accumulated in the Baker yeast cells. Accumulation increased with increasing pH, incubation time, temperature, and amount of yeast. Sb(V) was undisturbed under the conditions of the test, indicating selective accumulation of Sb(III) (Perez-Corona et al. 1997).

5.4.2 Transformation and Degradation

Air. Little is known about the chemical forms and physical and chemical transformations of trace elements in the atmosphere. This is primarily because analytical methods provide information concerning the metal content rather than the specific compounds or species. In the absence of specific information, it is generally assumed that elements of anthropogenic origin, especially those emanating from combustion sources, are present as the oxide. Windblown dust particles may contain antimony in mineral species, such as sulfides and oxides, and are associated with silicates. When released into the atmosphere as an aerosol, antimony is believed to be oxidized to antimony trioxide by reaction with atmospheric oxidants.

Water. Most of the dissolved antimony in natural waters is present in the pentavalent oxidation state as the antimonate species ($Sb(OH)_6^-$) under aerobic conditions (Filella et al. 2002). Anthropogenic emissions commonly contain antimony in the trivalent oxidation state (antimonite; e.g., antimony trioxide); however, it is not certain how quickly antimonite oxidizes to antimonate under natural conditions. Under anoxic reducing conditions, trivalent species, such as $Sb(OH_3)$, $Sb(OH_4)^-$ and $Sb_2S_4^-$, are the most thermodynamically stable forms.

The pentavalent form was reported to be the predominant species in a study examining the behavior of antimony in oxic systems (Filella et al. 2002). The trivalent form was also found to be sometimes present in oxic systems; however, >10% of the total dissolved amount of antimony was rarely found to be in the trivalent form (Filella et al. 2009a). Antimony speciation in various types of natural waters was analyzed in a study conducted in Warsaw Poland. Of the 12 samples obtained from the different rivers, lakes, and ponds, the majority of the total antimony, or 96–99%, was in the pentavalent form (Garbos et al. 2000).

Han-Wen et al. (1982) estimated the rate of oxidation of the trivalent form to the pentavalent form by adding known quantities of each into lake water and waste water samples and studying the change in concentration with respect to time. The trivalent form of antimony in lake water and waste water appeared to be unstable since none could be detected after 6 hours; it is presumed that there were oxidants in the water samples. The addition of tartaric acid (1% w/v) into the water samples had a stabilizing effect (no changes in Sb(III) levels) after 5 days due to the fact that the rate of conversion of Sb(III) into Sb(V) decreases with increasing acidity.

Cutter (1992) estimated a much slower oxidation rate of trivalent antimony in seawater by measuring the depth profiles for antimony species in the upper 100 m of the Black sea. No Sb(III) was detected in the upper surface levels, but a gradual increase of Sb(III) concentration with a gradual decrease in Sb(V) levels was observed with increasing depth beyond 60 m. The maximum concentration of Sb(III) was observed in the largely anaerobic region (90–100 m). At this depth, no pentavalent antimony was detectable. An estimated pseudo first-order oxidation rate constant of 0.008 day^{-1} was calculated from these data, corresponding to a residence time (1/rate constant) of about 125 days. This rate included all forms of removal since Sb(III) may also be scavenged by suspended particulate matter in the water column. It is presumed that the presence of the thermodynamically unstable trivalent species in aerobic waters may, in part, be due to biotic processes involving the uptake of antimonate and the subsequent biological conversion to the trivalent species. These unstable species were reported to be able to persist due to the low rates of conversion (Cutter 1992). Likewise, as the trivalent species may be present in thermodynamically unfavorable (aerobic) environments, the pentavalent species has also been detected in anoxic settings. As reported by Cutter (1992), the presence of pentavalent antimony in anoxic waters of the Baltic Sea, the Black Sea, and the Saanich Inlet has been observed, and is due to the transport of Sb(V) on sinking detritus from aerobic waters, formation of thioantimonate species, and advection of surface waters containing high levels of pentavalent antimony. All of these potential transport processes also assume a slow reduction rate of pentavalent conversion to the trivalent form. The rate constant for this reaction was estimated as $1.1x10^{-6}$ $days^{-1}$ (Cutter 1992).

Antimony can be reduced and methylated by microorganisms in the aquatic environment, similar to arsenic, and become mobilized (Andreae et al. 1983; Austin and Millward 1988). This reaction is most likely to occur in reducing environments, such as in bed sediment.

Pseudomonas fluorescens K27, isolated from the Kesterson reservoir in California, was found to reduce trimethyldibromoantimony to trimethylstibine (Bentley and Chasteeen 2002). Sb(III) and methylated antimony species were converted to stibine at approximately pH 7; however, Sb(V) was not converted. Sb(III) was found to be oxidized in an *Agrobacterium tumefaciens* isolate. The algal strain 5508, found at the Yellowstone National Park in the geothermal environment of Dragon Spring, was also found to have the capability to oxidize Sb(III) (Lehr et al. 2007).

The oxidation rate of As(III) and Sb(III) was studied using circumneutral pH (pH 5.5–6.5) and acidic conditions similar to those in mine tailings under both abiotic and biotic conditions. Under acidic conditions, both antimony and arsenic were slowly oxidized, but more rapid oxidation was observed in

aerated abiotic solutions containing Fe(III) as opposed to solutions containing microbes; this process was accelerated by natural sunlight and increasing chloride ion concentration (Asta et al. 2012). In unfiltered (microbially active) circumneutral water, antimony was oxidized at a similar rate as in the acidic solutions; however, the rate of arsenic oxidation was enhanced and was several orders of magnitude greater than the rate of antimony oxidation.

Sediment and Soil. Transformation of antimony in the soil is dependent on the microbial population (Luo et al. 2014). Anaerobic microbial methylation occurs in the soil, producing trimethylstibine. Trimethylstibine was produced by the pure cultures of *Clostridium collagenovorans* and *Desulfovibrio vulgaris* under anaerobic conditions in sewage sludge. Anaerobic digestion of sewage sludge by *Methanobacterium formicicum* formed stibine, monomethylstibine, dimethylstibine, and trimethylstibine (Michalke et al. 2000). Under aerobic conditions, *Scopulariopsis brevicaulis* was found to methylate antimony through a dimethylantimony species intermediate in the trimethylstibine pathway (Bentley and Chasteen 2002).

Five soil samples were collected in an antimony and arsenic mine field in the Hunan Province of China. It was determined that *Gemmatimonadetes* and *Actinobacteria* aid in the bioremediation of antimony in the mine field soil (Luo et al. 2014).

Other Media. A 1998 study detected antimony in infant cot mattress covers that contained polyvinyl chloride (PVC). Antimony leached into extraction fluids from mattress samples (Jenkins et al. 1998). In the mid-1990s, it was hypothesized that microbial growth on the cot mattress could generate stibines from the antimony trioxide in the flame retardants. It was also hypothesized that the stibine could result in sudden infant death syndrome (SIDS) (Richardson 1994). However, increases in liver and brain antimony levels have not been found in infants dying from SIDS, as compared to infants dying from other causes (Boex et al. 1998; Cullen et al. 2000).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to antimony depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of antimony in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on antimony levels monitored or estimated in the

environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-6 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-7.

Table 5-6. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.004 µg	De Doncker et al. 1983
Drinking water	0.5 µg/L Sb(V), 0.9 µg/L Sb(III)	Vinas et al. 2006
Surface water and groundwater	0.00001 µg	de la Calle-Guntinas et al. 1991
Soil and sediment	0.03 µg/g	Lopez-Garcia et al. 1997
Whole blood, tissue, or hair	No data	NIOSH 1985
Urine	0.01 µg/L	Quiroz et al. 2011

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-7. Summary of Environmental Levels of Antimony

Media	Low	High	For more information
Ambient air (ppbv)	0	24.917 (median)	Table 5-9
Ground water (ppb)	<1	12 (geometric mean)	Section 5.5.2
Soil (ppm)	<1	8.8	Section 5.5.3

Detections of antimony in air, water, and soil at NPL sites are summarized in Table 5-8.

Table 5-8. Antimony Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	60.5	87.1	5.81	158	104
Soil (ppb)	53,200	75,700	9.05	278	161
Air (ppbv)	0.00623	0.0237	22.3	12	10

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Background levels of antimony in ambient air are usually on the order of about 1 ng/m^3, but can be higher in urban environments. In the vicinity of plants that convert antimony ores into metal (smelting operations), or other point sources, levels can be >1,000 ng/m^3.

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and HAPs monitoring data. Detailed air monitoring data for antimony in various cities in the United States for 2014 are shown in Table 5-9. Data for other years are available and may be accessed directly from the EPA website. Daily mean concentrations ranged from 0.37 to 2 ng/m^3 for antimony (total suspended particulate; TSP) standard temperature and pressure (STP); 0.13–20.6 ng/m^3 for antimony PM_{10} LC (local conditions); 0.56–2.18 ng/m^3 for antimony PM_{10} STP; and 1.9–22 ng/m^3 for antimony $PM_{2.5}$ LC (EPA 2015).

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony (TSP) STP	Rosemount, Minnesota	27	0
	Eagan, Minnesota	26	1.429
	Eagan, Minnesota	28	2
	Apple Valley, Minnesota	25	0.417
	Minneapolis, Minnesota	24	1.6
	Minneapolis, Minnesota	25	0.385
	Minneapolis, Minnesota	26	0.37
	Minneapolis, Minnesota	27	0
	St. Paul, Minnesota	27	0

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Virginia, Minnesota	27	0
	Duluth, Minnesota	22	0.4
	Duluth, Minnesota	25	0.4
	Newport, Minnesota	25	0
	Bayport, Minnesota	27	0
	Yukon, Oklahoma	28	0.425
	Oklahoma City, Oklahoma	40	0.5
	Tulsa, Oklahoma	40	0.667
	Tulsa, Oklahoma	39	0.59
	Tulsa, Oklahoma	39	0.789
	Tulsa, Oklahoma	38	0.784
Antimony PM_{10} LC	Phoenix, Arizona	44	2.450909
	Middletown, California	45	4.511111
	Cobb, California	45	4.444444
	Banning, California	10	1.05
	San Jose, California	45	2.463111
	Valrico, Florida	15	1.46
	Valrico, Florida	15	1.58
	Boston, Massachusetts	39	1.51
	Boston, Massachusetts	23	1.49087
	St. Louis, Missouri	3,705	20.64183
	St. Louis, Missouri	40	1.74975
	St. Louis, Missouri	40	1.7335
	Underhill (Town of), Vermont	14	0.133571
	Underhill (Town of), Vermont	3	0.25
	Seattle, Washington	40	1.0185
Antimony PM_{10} STP	Orlando, Florida	22	0.754545
	Saint Petersburg, Florida	43	0.635349
	Pinellas Park, Florida	45	0.697556
	Northbrook, Illinois	27	0.681111
	Ashland, Kentucky	34	2.182353
	Ashland, Kentucky	2	1.3
	Kentucky	33	0.562727
	Kentucky	15	1.012667
	Lexington-Fayette (corporate name for Lexington), Kentucky	33	1.047879
	Kentucky	34	0.754118
	Calvert City (RR name Calvert), Kentucky	32	0.59375
	Providence, Rhode Island	50	0.6466

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Providence, Rhode Island	24	0.631667
	Houston, Texas	88	0.647727
Antimony $PM_{2.5}$ LC	Birmingham, Alabama	80	19.213
	Birmingham, Alabama	76	18.539
	Huntsville, Alabama	39	20.115
	Montgomery, Alabama	41	17.768
	Phenix City, Alabama	41	20.732
	Fairbanks, Alaska	82	19.854
	Fairbanks, Alaska	70	20.95
	Alaska	30	24.15
	Phoenix, Arizona	83	20.729
	Tucson, Arizona	71	21.092
	North Little Rock, Arkansas	81	20.259
	Chico, California	47	10.383
	Fresno, California	80	20.344
	Calexico, California	39	15.897
	Los Angeles, California	81	19.722
	Portola, California	45	11.044
	Rubidoux, California	79	19.241
	Rubidoux, California	41	18.683
	Arden-Arcade, California	84	19.929
	Sacramento, California	46	12.109
	El Cajon, California	17	19.529
	Escondido, California	47	10.723
	San Jose, California	72	19.326
	Modesto, California	47	12.213
	Visalia, California	47	11.106
	Commerce City, Colorado	38	18.579
	Colorado	69	20.457
	Platteville, Colorado	35	17.529
	New Haven, Connecticut	68	18.904
	Dover, Delaware	13	19.615
	Wilmington, Delaware	62	18.468
	Washington, District Of Columbia	78	22.045
	Davie, Florida	45	18.944
	Valrico, Florida	79	20.101
	Tallahassee, Florida	39	18.923
	Pinellas Park, Florida	39	20.244
	Macon, Georgia	42	18.429

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Athens (corporation name Athens-Clarke County), Georgia	42	22.083
	Georgia	42	21.643
	Georgia	68	19.478
	Georgia	40	20.05
	Columbus (Remainder), Georgia	41	22.695
	Augusta-Richmond County (Remainder), Georgia	34	21.382
	Georgia	41	19.805
	Hawaii	66	19.712
	Idaho	80	20.438
	Chicago, Illinois	42	22.405
	Chicago, Illinois	75	20.907
	Northbrook, Illinois	74	18.507
	Naperville, Illinois	38	18.013
	Granite City, Illinois	22	20.75
	Roxana, Illinois	39	19.692
	Belleville, Illinois	38	20.605
	Jeffersonville, Indiana	41	19.22
	Jasper, Indiana	41	20.232
	Elkhart, Indiana	41	18.963
	Middletown, Indiana	41	19.402
	Gary, Indiana	39	19.372
	Indianapolis (Remainder), Indiana	60	20.192
	Evansville, Indiana	42	18.774
	Cedar Rapids, Iowa	41	18.159
	Des Moines, Iowa	41	18.11
	Davenport, Iowa	81	20.302
	Wichita, Kansas	42	19
	Kansas City, Kansas	69	20.645
	Ashland, Kentucky	42	20.571
	Kentucky	41	17.5
	Lexington-Fayette (corporate name for Lexington), Kentucky	42	19.726
	Louisville, Kentucky	81	20.951
	Shreveport, Louisiana	39	18.205
	Baton Rouge, Louisiana	76	18.941
	Essex, Maryland	75	19.687
	Beltsville, Maryland	82	21.451
	Chicopee, Massachusetts	80	20.819

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Boston, Massachusetts	84	20.077
	Boston, Massachusetts	42	18.333
	Grand Rapids, Michigan	82	20.951
	Tecumseh, Michigan	42	19.583
	Michigan	42	20.952
	Michigan	42	19.512
	Port Huron, Michigan	42	20.298
	Allen Park, Michigan	81	20.062
	Detroit, Michigan	41	18.402
	Dearborn, Michigan	42	18.607
	Blaine, Minnesota	82	20.043
	Minneapolis, Minnesota	83	20.596
	Rochester, Minnesota	42	19.738
	Jackson, Mississippi	66	20.818
	Missouri	82	22.079
	Arnold, Missouri	82	20.152
	Missouri	78	21.269
	St. Louis, Missouri	81	20.16
	Montana	68	19.096
	Butte-Silver Bow (Remainder), Montana	53	19.519
	Omaha, Nebraska	71	19.873
	Sunrise Manor, Nevada	70	19.514
	Reno, Nevada	66	19.955
	Camden, New Jersey	68	19.831
	Newark, New Jersey	68	20.368
	North Brunswick Township, New Jersey	66	20.515
	North Brunswick Township, New Jersey	38	18.842
	Chester, New Jersey	68	19.625
	Elizabeth, New Jersey	69	18.725
	Albuquerque, New Mexico	84	19.5
	Albany, New York	79	18.025
	New York, New York	72	18.535
	Buffalo, New York	38	18.526
	New York	42	19.274
	Rochester, New York	80	22.65
	New York, New York	82	19.024
	New York, New York	84	19.964
	New York	80	20.556
	Asheville, North Carolina	29	17.534

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Hickory, North Carolina	12	24.917
	Lexington, North Carolina	40	18.838
	Winston-Salem, North Carolina	38	19.842
	Charlotte, North Carolina	84	19.143
	Rockwell, North Carolina	42	18.202
	Raleigh, North Carolina	78	19.391
	North Dakota	84	19.048
	Cleveland, Ohio	38	22.013
	Cleveland, Ohio	66	21.356
	Cleveland, Ohio	36	20.75
	Columbus, Ohio	42	18.75
	Cincinnati, Ohio	83	19.88
	Steubenville, Ohio	36	19.944
	Ironton, Ohio	42	19.048
	Sheffield, Ohio	41	22.61
	Toledo, Ohio	37	18.432
	Youngstown, Ohio	30	19.333
	Dayton, Ohio	36	18.819
	New Paris, Ohio	83	20.524
	Canton, Ohio	41	19.341
	Akron, Ohio	35	19.243
	Oklahoma City, Oklahoma	40	18.538
	Tulsa, Oklahoma	81	19.914
	Altamont, Oregon	26	13.596
	Altamont, Oregon	3	11.6
	Lakeview, Oregon	30	13.482
	Lakeview, Oregon	3	11.6
	Eugene, Oregon	30	12.715
	Eugene, Oregon	3	11.583
	Portland, Oregon	71	19.993
	Pennsylvania	41	20.378
	Pittsburgh, Pennsylvania	70	19.164
	Liberty, Pennsylvania	42	20.024
	Pennsylvania	42	19.369
	Johnstown, Pennsylvania	42	17.119
	State College, Pennsylvania	37	20.378
	Pennsylvania	28	17.732
	Pennsylvania	40	18.8
	Erie, Pennsylvania	40	20.2

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Scranton, Pennsylvania	22	18.25
	Lancaster, Pennsylvania	42	20.75
	Freemansburg, Pennsylvania	37	18.541
	Philadelphia, Pennsylvania	79	21.285
	Philadelphia, Pennsylvania	42	19.607
	Pennsylvania	39	18.128
	Greensburg, Pennsylvania	38	18.684
	York, Pennsylvania	41	21.561
	East Providence, Rhode Island	80	19.894
	South Carolina	36	17.597
	Greenville, South Carolina	39	19.936
	Dentsville (Dents), South Carolina	83	19.602
	Sioux Falls, South Dakota	74	19.818
	Nashville, Tennessee	41	21.988
	Chattanooga, Tennessee	42	19.512
	Knoxville, Tennessee	40	20.3
	Loretto, Tennessee	41	20.988
	Memphis, Tennessee	79	18.899
	Dallas, Texas	86	2.033
	Dallas, Texas	82	20.683
	Midlothian, Texas	44	2.002
	El Paso, Texas	75	21.407
	Texas	46	1.972
	Deer Park, Texas	83	19.813
	Deer Park, Texas	42	18.595
	Texas	41	18.817
	Corpus Christi, Texas	42	1.993
	Bountiful, Utah	41	18.512
	Salt Lake City, Utah	74	21.378
	Lindon, Utah	41	22.854
	Burlington, Vermont	56	20.813
	East Highland Park, Virginia	62	19.435
	Vancouver, Washington	42	19.488
	Seattle, Washington	77	20.052
	Tacoma, Washington	39	17.731
	Marysville, Washington	38	20.763
	Yakima, Washington	42	19.952
	West Virginia	70	19.636
	South Charleston, West Virginia	13	18.846

Table 5-9. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
	Moundsville, West Virginia	27	18.185
	Green Bay, Wisconsin	41	18.951
	Horicon, Wisconsin	84	19.75
	Milwaukee, Wisconsin	79	19.101
	Wisconsin	42	18.881
	Waukesha, Wisconsin	41	20.061
	Wyoming	82	19.384

LC = local conditions; PM = particulate matter; STP = standard temperature and pressure; TSP = total suspended particulate

Source: EPA 2015

Antimony concentrations over the North Atlantic and North Pacific were 0.086 and 0.0037 ng/m^3, respectively (Arimoto and Duce 1987; Austin and Millward 1988). Two values reported for antimony in aerosols in clean continental and marine environments were 0.2 ng/m^3 at the Jungfraujoch in the Swiss Alps and 0.00045 ng/m^3 at American Samoa (Austin and Millward 1988). The MMAD of antimony-containing aerosols from a range of areas remote from anthropogenic sources was 0.86 μm (Milford and Davidson 1985). The mass size distribution is bimodal, with the larger peak at about 0.6 μm and a smaller one at about 3 μm. An example of the size distribution of antimony-containing particles removed from anthropogenic sources was obtained in an 8-week study on an island in the German Bight. The concentration of antimony in a size fraction increased as the size decreased. The antimony concentration ranged from 0.03 ng/m^3 for particles >7.2 μm to 0.3 ng/m^3 for particles <0.5 μm (Stoessel and Michaelis 1986).

Antimony is enriched in coal and vaporized in fossil fuel combustion, resulting in the release of increased levels of antimony to the atmosphere. After condensation, antimony is primarily found in fly ash (Miravet et al. 2006). Antimony levels in coal fly ash leachates from two different samples obtained from the Escucha coal-fired power station in Teruel, Spain were reported to be 0.01–0.07 μg/g for Sb(III) and 0.17–0.41 μg/g for Sb(V) in the first sample. Levels were slightly higher in the second sample: Sb(III) levels were 0.02–0.09 μg/g and Sb(V) levels were 0.16–0.56 μg/g. The data indicate that Sb(V) was the predominant species found in the leachate, and while the antimony was found to bind strongly to the matrix, the study demonstrated that significant amounts of antimony can leach out of coal fly ash particles (Miravet et al. 2006). Likewise, in Taipei, Taiwan, the total antimony content in fly ash was 4.7 μg/g,

while in Barcelona, Spain, the Sb(III) content was 0.07–0.36 µg/g and the Sb(V) content was 1.63 µg/g. Antimony content (predominantly Sb(III)) in fly ash from various countries ranged from 1 to 3.9 µg/g (Smichowski 2008). Antimony emissions may have increased in Japan over the years due to the fact that part of the process in the incineration of household wastes containing plastics occurs in Japan; thus, fly ash originating from waste incineration may be an important source of antimony (Iijima et al. 2009).

Several older studies show that antimony can travel long distances, and that ambient levels may reflect the origin of the air masses. The geometric mean antimony concentrations in aerosols at three rural/ remote locations in New York State were 1.0, 0.72, and 0.33 ng/m^3 (Dutkiewicz et al. 1987), and the enrichment over crustal abundance ranged from 920 to 1,650. The enrichment factor is smaller but similar to the mean enrichment factor of 1,880 for antimony in 29 cities (Gladney et al. 1984). The high enrichment indicates that the antimony is of anthropogenic origin. An analysis of the New York State data using backward-in-time air trajectories is consistent for the Midwest being the dominant source of antimony. An analysis of European sources and wind trajectories further illustrate that antimony may be transmitted over long distances. The average concentrations at a city in southern Norway were 0.54 ng/m^3 when the air masses came from the United Kingdom and 0.07 ng/m^3 when they came from over the Atlantic (Hillamo et al. 1988).

Twenty-four-hour samples collected at 10 locations in Washington, DC yielded average antimony concentrations ranging from 1.1 to 3.0 ng/m^3 (Kowalczyk et al. 1982). As a result of a chemical element balance analysis, the three major contributing sources in order of decreasing significance are believed to be refuse incineration, motor vehicles, and coal combustion. In a Houston study, the range of antimony concentrations in fine (0.1–2.5 µm) aerosols was 0–12 ng/m^3, whereas in particles >2.5 µm, the range was 0–4 ng/m^3 (Johnson et al. 1984). Median, mean, and maximum concentrations of antimony in aerosols at three sites in Quebec, Ontario, and Nova Scotia were 0.05–0.10, 0.11–0.23, and 0.37–2.17 ng/m^3, respectively (Hopper and Barrie 1988). According to the Texas Air Control Board, the first- and second-highest annual average antimony concentrations in Texas between 1978 and 1982 were 452 and 50 ng/m^3 at Laredo and Dallas, respectively. The statewide 1978–1982 average was below the minimum detectible mean of 90 ng/m^3 (Wiersema et al. 1984).

Concentrations of antimony in 24-hour air samples at Kellogg, Idaho, an area with a large number of operating mines, ranged from 5.21 to 1,210 ng/m^3, with a mean of 146 ng/m^3 (Ragaini et al. 1977). The 6-month average concentration of antimony in air in an industrial area of England where a number of ferrous and nonferrous metal smelting and manufacturing works were concentrated was 40 ng/m^3. This is

a factor of 50 higher than that found in rural areas (Pattenden et al. 1982). The maximum concentration at the industrial site was 69 ng/m^3.

The mean monthly concentration of antimony in precipitation at Birkenes in southern Norway ranged from 0.2 to 2.3 µg/L, with a mean of 0.6 µg/L (Pacyna et al. 1984). During the same period, the respective air concentrations were 0.19–0.80 and 0.43 ng/m^3. Rain samples were collected during two storms upwind and downwind of a copper smelter in Tacoma, Washington. Antimony in rainwater originated primarily from the smelter. The mean total antimony concentration in rainwater downwind from the smelter was 1.3 µg/L; the concentration upwind was 0.03 µg/L (Vong et al. 1988). Eighty percent of the antimony in rainwater was dissolved (i.e., passed through a 0.45-µm filter).

Antimony is almost entirely found in the particulate, as opposed to the dissolved fraction of snow (Landsberger et al. 1983). The antimony content of snow particulate matter in samples from Montreal, Canada, ranged from 4 to 145 ppm. Another sampling of snow around Montreal found total antimony concentrations of 1–8.7 ppb and enrichment factors of 39–590 (Zikovsky and Badillo 1987).

Antimony is a component of ammunition, and studies have been performed to ascertain the elemental concentrations of antimony in the air of indoor shooting ranges. Antimony might be expected in such situations because it is alloyed with lead in bullets, and lead stibnite and antimony sulfides are used as primers (Dams et al. 1988). After an intensive 3-hour shooting exercise, levels of antimony reached 119 µg/m^3 (190,000 ng/m^3), or 4 orders of magnitude over ambient levels (Vandecasteele et al. 1988). An instructor at the shooting range had a time-weighted average (TWA) inhalable antimony concentration of 12.0 µg/m^3 (1,200 ng/m^3) compared with the threshold limit value (TLV) of 500 µg/m^3 (500,000 ng/m^3). An American study conducted at the National Guard Armory in Washington, DC, during routine daytime and gun club use, found indoor antimony concentrations ranging from 57 to 216 µg/m^3 (57,000–216,000 ng/m^3) versus background air ranging from 1.5 to 2.3 µg/m^3 (1,500–2,300 ng/m^3), an enrichment of 9,900 over District of Columbia air (Olmez et al. 1985). More than 60% of the antimony was associated with respirable particles with an aerodynamic diameter <3.5 pm (<3,500 ppb).

5.5.2 Water

The National Water-Quality Assessment (NAWQA) program surveyed groundwater across the United States from 1992 to 2003 and generally found low concentrations of antimony in the water. Median concentrations were reported as <1 µg/L (ppb) (USGS 2011). Other studies also reported low

concentrations of antimony in water. Eckel and Jacob (1989) gathered water monitoring data from the Water Resources Division of the U.S. Geological Survey (USGS) covering the period from about 1960 to September, 1988, and found that all but 70 of 1,077 entries for dissolved antimony were below 5 µg/L. The geometric mean and standard deviation of the 70 values >5 µg/L were 12 and 1.93 µg/L, respectively. The concentrations of dissolved antimony were 1.62 nM (0.197 µg/L) in the St. Lawrence River at Massena, New York and 2.73 nM (0.332 µg/L) in the Yukon River. European rivers had dissolved antimony at concentrations ranging from <0.03 to 4.43 nM (0.004–0.539 µg/L) (Andreae and Froelich 1984).

Geothermal waters often have naturally elevated levels of trace metals such as arsenic, mercury, and antimony. The speciation of these compounds is complex and can change during sampling, storage, and analysis; therefore, results are usually reported as the total amount present in the geothermal water. Analysis of 268 thermal springs in Yellowstone National Park showed total antimony levels ranging from 9 to 166 µg/L for sampling conducted from 1966 to 1975 (Stauffer and Thompson 1984). USGS (2010) analyzed water samples from streams, tributaries, drainage channels, and other water bodies at 104 locations in the Yellowstone National Park, Wyoming from 2006 to 2008. The results of this study are summarized in Table 5-10.

Table 5-10. Total Antimony Levels in Water Samples Collected at Yellowstone National Park

Sampling location	Antimony (µg/L)
Norris-Mammoth Corridor and West Nymph Creek	<1–6
Norris Geyser Basin	<1–180
Gibbon Canyon and Geyser Springs Group	3–95
Crater Hills area	1–150
Ojo Caliente Spring and its discharge channel, Lower Geyser Basin	10–94
Porcupine Hills area	62–123
Midway Geyser Basin and the Rabbit Creek area	0–82
Mud Volcano area	<0.5–6
Washburn Hot Springs	<0.5

Source: USGS 2010

These data are consistent with antimony levels in geothermal waters in other parts of the world. For example, antimony levels ranged from 0.05 to 244 µg/L (n=75), with a mean value of 35 µg/L for geothermal waters sampled in various locations of Japan.

Anthropogenic activity can result in elevated levels of antimony in nearby water systems. A study in Luxembourg found higher concentrations of antimony in samples close to an ore site as compared to concentrations further from the site (Filella et al. 2009b). Similarly, a study in Corsica found higher levels of antimony in the water after crossing the mining soils, with concentrations decreasing further downstream (Migon and Mori 1999).

Sb(V) was the most prevalent species of antimony found in drinking water. Sb(V) is expected to predominate due to the oxidative treatments used in water disinfection processes (Belzile et al. 2011). Sb(V) was also the predominant species in oceans at mean concentrations of 200 ng/L. Sb(V) is predominant in oxic and mildly reducing environments. Sb(III) is predominant in anoxic waters and porewaters, and in reducing conditions. The presence of thermodynamically unfavorable Sb(III) in oxygenated surface waters has been attributed largely to phytoplankton activity (Chen et al. 2003).

The major antimony mining area in the United States was the Kellogg district in northern Idaho, and mining and smelting wastes have been dumped into the South Fork of the Coeur d'Alene River for over 80 years (Mok and Wai 1990). The South Fork joins with the North Fork of the river to form the Main Stem of the Coeur d'Alene River somewhat below Kellogg. Mean and maximum total dissolved antimony concentrations at two sites on the South Fork were 4.3 and 8.2 µg/L, respectively. Mean and maximum concentrations at six stations on the Main Stem ranged from 0.6 to 1.0 and from 0.8 to 1.9 µg/L, respectively. Those at a station on the unpolluted North Fork were 0.09 and 0.2 µg/L, respectively.

Since antimony is used in solder, there has been interest as to whether antimony will leach from pipes soldered with antimony-containing solder into drinking water. Leaching of antimony from tin/antimony (Sn/Sb) solder when it comes in contact with water with pH of 5.2–8.6 was evaluated using loops of pipe containing 20 solder joints (Murrell 1987). Antimony was undetectable (<4 ppb) in the water at first, but rose to 10 ppb after 4 days and 68 ppb (at pH 7.4) after 4 weeks. A study was conducted at the University of Washington to evaluate the potential for leaching of metals into drinking water from 95/5 Sn/Sb solder (EPA 1982). After a series of static and continuous-flow laboratory tests and evaluation of field samples from university buildings, it was concluded that increases in antimony concentration as a result of corrosion and leaching were minimal and would not contribute significantly to dietary antimony intake. Only one of the field samples of standing water from university buildings containing Sn/Sb solder joints was above the detection limit of 0.6 ppb. The sample contained 2 ppb of antimony, one-half of which

was dissolved. Examination of the solder joints indicated that a double passivation film of tin monoxide (SnO) and tin dioxide (SnO_2) forms and inhibits leaching.

5.5.3 Sediment and Soil

Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 µg/g (ppm), but these levels vary by location (Telford et al. 2008). A survey of soils throughout the conterminous United States conducted by the USGS showed that antimony concentrations ranged from <1 to 8.8 ppm (µg/g) with an average concentration of 0.48 ppm (µg/g). This was the third lowest concentration of the 50 elements surveyed (DOI 1984). In this survey, samples were taken at a depth of 20 cm at 1,318 sampling sites. Soils not derived from ore-bearing rock or close to industrial sources do not generally contain more than 1 ppm (µg/g) of antimony. Background concentrations for antimony in soil ranged from 0.06 to 0.79 µg/g in seven Florida soil orders. Concentrations were dependent on the location, mineralization, parent material differences, varying degrees of anthropogenic influence, and different sampling strategies (Wilson et al. 2010). Elevated levels of antimony in soil samples are commonly associated with anthropogenic activities such as mining, fossil fuel combustion, smelting, and other activities. Samples of soil were collected from the decommissioned Hanford Site along the Columbia River in 2008. The Hanford site was utilized to produce plutonium. Antimony was detected in 27 out of 158 samples at a mean concentration of 0.113 µg/g. Antimony and selenium were not able to be detected in the majority of the samples (DOE 2009b). The distribution of antimony at two sites in Austria, with close proximity to traffic routes, was evaluated by Amereih et al. (2005) at two sampling depths (0–5 and 5–10 cm from the soil surface) and three distances (0.2, 2, and 10 m) from the edge of the road. In addition to roadside soil, samples were also obtained from Lungau, an alpine region with negligible traffic. Table 5-11 summarizes the results from this study during two sampling periods (2002 and 2005).

Table 5-11. Antimony Levels at Three Locations With Different Vehicular Traffic

Location[a]	Distance from road (m)	Sample depth (cm)	Total Sb µg/g (2002)	Total Sb µg/g (2005)
Lungau	Not applicable	0–5	0.64	Not available
	Not applicable	5–10	0.81	Not available
Knittelfeld	0.2	0–5	6.30	8.68
	0.2	5–10	3.80	4.78
	2	0–5	1.75	1.99
	2	5–10	1.51	1.96
	10	0–5	1.21	1.16
	10	5–10	1.13	1.13

Table 5-11. Antimony Levels at Three Locations With Different Vehicular Traffic

Location[a]	Distance from road (m)	Sample depth (cm)	Total Sb µg/g (2002)	Total Sb µg/g (2005)
Rankweil	0.2	0–5	2.74	Not available
	0.2	5–10	1.83	Not available
	2	0–5	1.52	Not available
	2	5–10	1.21	Not available
	10	0–5	0.91	Not available
	10	5–10	0.82	Not available

[a]Vehicular traffic at the Knittelfeld and Rankweil sampling locations exceeds 20,000 vehicles per day, while there is no vehicular traffic at the Lungau location.

Source: Amereih et al. 2005

Examining the monitoring data from this study shows clear trends in the antimony levels in the soils reflective of anthropogenic contributions due to the presence of motor vehicles at the Knittelfeld and Rankweil locations as compared to the site with negligible vehicular traffic. Moreover, greater antimony levels are observed at both sampling depths the nearer to the road the soil samples were obtained (0.2 versus 2 versus 10 m). Levels of antimony decreased to near background levels within a few meters from the edge of the road.

High concentrations of antimony were observed in soil at a shooting range. Antimony concentrations (only Sb(V)) were 4,000 µg/g in soil samples collected at a depth of 1 cm, 1,600–17,500 µg/g in soil samples collected at 0–5 cm, 3,400 mg/kg at 5–15 cm, 1,300 µg/g at 16 cm, and 8,600 µg/g at 25–45 cm at different sites at the shooting range (Scheinost et al. 2006). In a study of small arms ranges at military sites in eight U.S. states, antimony levels ranged from 7 to 91 µg/g in composite samples of the top few inches of soil (Bannon et al. 2009).

Levels of mean antimony, Sb(III), and Sb(V) in contaminated soils from the Hillgrove mine located in New South Wales, Australia were measured in six samples. This facility mines for gold and antimony and has been in operation for over 100 years. There were higher levels of Sb(V) than Sb(III) in the soil samples, ranging from 12 to 27 µg/g for Sb(III) and from 211 to 384 µg/g for Sb(V). Total mean antimony levels ranged from 470 to 849 µg/g (Telford et al. 2008). Concentrations of antimony were also high in the sediment around mining sites in Corsica. The levels of antimony decreased with increasing distance downstream from the site. Concentrations ranged from 8 to 1,108 µg/g in January 1993 and from 10 to 1,005 µg/g in March 1993 depending upon the sampling location (Migon and Mori 1999).

The greatest concentrations occurred at a sampling location on the Presa River nearby the mine and gradually decreased at sampling locations 10 km away where the Presa River runs into the Bravona River.

Levels of Sb(III), Sb(V), and total antimony were monitored at three locations in sediment from the Plawniowice reservoir in Poland nearby metallurgy and coal mining operations (Jablonska-Czapla et al. 2014). Levels of Sb(III) varied between approximately 20–45 µg/g in the upper (0–5 cm) sediment profile and approximately 20–35 µg/g in sediment collected from a depth of 15–20 cm. Sb(V) levels were similar in both the upper sediment samples and the lower sediment samples with levels ranging from approximately 5 to 25 µg/g.

5.5.4 Other Media

Antimony trioxide (Sb_2O_3) is used in the production of PET. The antimony content in PET has been reported to be as high as 190–300 mg/kg. Leaching of antimony into PET water bottles has been reported in several studies of water bottles and food storage containers produced in the United States, Mexico, and Europe (Belzile et al. 2011; Chapa-Martinez et al. 2016; Westerhoff et al. 2008). These studies have shown that increased temperature and length of time stored may contribute to more antimony being released from the containers. Belzile et al. (2011) reported that the levels of antimony increased from 200 to 7,800–9,700 ng/L in heated water bottles (at 80°C for 48 hours). Heated PET packing materials had antimony concentrations ranging from 50 to 285 mg/kg and non-heated containers had levels <0.1–24 µg/kg. Concentrations of antimony in food has been reported to be <1.0 µg/g (Belzile et al. 2011). At room temperature, only a small amount of antimony was detected in U.S. bottled water (average concentration of 0.195 ppb) (Westerhoff et al. 2008).

Antimony has been detected in commercial juices. Juices of blackcurrant, mixed fruit, strawberry, raspberry, sour cherry, mint, and synthetic caramel purchased from Greece, Denmark, and Scotland were analyzed for antimony content. The highest concentration of antimony from the 42 samples was 13.6 µg/L, reported in sour cherry juice packaged in glass (Hansen et al. 2010).

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to antimony through ingestion of food and drinking water, inhalation of particulates from ambient air, or ingestion of contaminated soil or dust. Occupational

exposures of antimony may occur at smelters, coal-fired plants, and refuse incinerators that process or release antimony.

In discussing exposure to antimony, it is important to consider what form of antimony a person is exposed to and its availability. High concentrations of antimony may be found in the contaminated soil and sediment. In water, the pentavalent state is predominant, although significant levels of trivalent antimony and methylated antimony compounds exist. People who live or work near sources of antimony such as smelters, coal-fired power plants, and refuse incinerators may be exposed to high levels of antimony in airborne dust, soil, and vegetation. People who live near or work at waste sites that receive slag from smelters or fly ash from power plants and refuse incinerators may also be exposed to higher than background levels. Exposure routes would include either inhalation of contaminated air or ingestion of contaminated soil or vegetation. Similarly, people who are exposed to soot and smoke in fires, such as firefighters, may be exposed to high levels of antimony. Occupational exposure to antimony appears to be highest for those involved in the production and processing of antimony and antimony oxide. Workers in battery-forming areas of lead-storage battery plants may be exposed to high levels of stibine.

In the Fourth National Report on Human Exposures to Environmental Chemicals reported by the Centers for Disease Control and Prevention (CDC 2019) results from the NHANES updated tables 1999–2016 were provided for antimony. Antimony levels in unadjusted urine (see Table 5-12), and creatinine corrected urine (see Table 5-13) were evaluated for a variety of age groups and ethnicities. Urinary samples reflect recent exposure to antimony (CDC 2019). The geometric mean and median concentrations of urinary antimony have dramatically decreased from 1999–2000 to 2005–2006 (40–50%); thereafter, the urinary antimony levels have only changed slightly (increased or decreased). These differences may be due to decreases in exposure or methodological differences.

Gebel et al. (1998b) investigated urine, blood, and scalp hair for antimony biomonitoring. No association between elevated soil levels and urinary antimony levels were found in this study of >200 German residents. A high proportion of blood samples had antimony levels below the limit of detection. Antimony was detected in hair samples from individuals in Rio de Janeiro at concentrations that ranged from <0.03 to <1.8 µg/g. The samples were for both men and women and were collected from the scalp in the occipital area (back of the head) (Miekeley et al. 1998). In an analogous study, the mean concentration of antimony in hair samples from 55 men and women from Scranton, Pennsylvania contained 0.096 ppm of antimony. The hair samples of populations from cities in four other countries contained mean antimony levels between 0.11 and 0.86 ppm (Takagi et al. 1986). A Japanese national

Table 5-12. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	0.132 (0.120–0.145)	0.130 (0.120–0.150)	0.220 (0.200–0.230)	0.330 (0.300–0.350)	0.430 (0.390–0.470)	2,276
	2001–2002	0.134 (0.126–0.142)	0.130 (0.130–0.140)	0.190 (0.180–0.200)	0.270 (0.250–0.310)	0.350 (0.320–0.400)	2,690
	2003–2004	*	0.080 (<LOD–0.090)	0.130 (0.120–0.150)	0.200 (0.190–0.220)	0.280 (0.250–0.320)	2,558
	2005–2006	0.073 (0.066–0.081)	0.070 (0.070–0.080)	0.120 (0.110–0.140)	0.220 (0.180–0.250)	0.300 (0.270–0.360)	2,576
	2007–2008	0.061 (0.057–0.066)	0.060 (0.060–0.060)	0.100 (0.090–0.110)	0.170 (0.140–0.200)	0.240 (0.220–0.260)	2,627
	2009–2010	0.056 (0.053–0.059)	0.050 (0.050–0.060)	0.090 (0.090–0.100)	0.170 (0.140–0.180)	0.230 (0.200–0.280)	2,847
	2011–2012	*	0.047 (0.042–0.052)	0.083 (0.075–0.091)	0.144 (0.125–0.158)	0.188 (0.169–0.222)	2,504
	2013–2014	0.043 (0.039–0.048)	0.041 (0.036–0.046)	0.076 (0.069–0.086)	0.130 (0.120–0.144)	0.189 (0.170–0.214)	2,664
	2015–2016	0.047 (0.044–0.051)	0.046 (0.043–0.051)	0.080 (0.077–0.085)	0.137 (0.126-0.150)	0.201 (0.171–0.218)	3,061
Age group							
3-5 years	2015–2016	0.049 (0.044–0.055)	0.049 (0.042–0.054)	0.087 (0.075–0.096)	0.138 (0.118–0.164)	0.188 (0.152–0.212)	486
6–11 years	1999–2000	0.176 (0.154–0.200)	0.190 (0.160–0.210)	0.260 (0.230–0.280)	0.350 (0.300–0.400)	0.440 (0.320–0.600)	316
	2001–2002	0.146 (0.134–0.160)	0.150 (0.130–0.160)	0.200 (0.180–0.210)	0.270 (0.240–0.330)	0.340 (0.280–0.440)	368
	2003–2004	0.099 (0.087–0.114)	0.100 (0.070–0.120)	0.160 (0.120–0.200)	0.240 (0.190–0.310)	0.310 (0.230–0.330)	290
	2005–2006	0.075 (0.063–0.088)	0.080 (0.060–0.090)	0.110 (0.090–0.130)	0.190 (0.120–0.260)	0.240 (0.170–0.340)	355
	2007–2008	0.068 (0.061–0.077)	0.070 (0.060–0.080)	0.110 (0.090–0.130)	0.170 (0.150–0.210)	0.230 (0.180–0.280)	394
	2009–2010	0.069 (0.061–0.079)	0.070 (0.060–0.080)	0.120 (0.100–0.150)	0.220 (0.150–0.260)	0.260 (0.230–0.350)	378
	2011–2012	0.064 (0.059–0.069)	0.059 (0.049–0.072)	0.108 (0.094–0.124)	0.169 (0.152–0.188)	0.206 (0.182–0.257)	399
	2013–2014	0.052 (0.045–0.060)	0.053 (0.046–0.065)	0.096 (0.089–0.105)	0.151 (0.128–0.172)	0.228 (0.168–0.254)	402
	2015–2016	0.061 (0.054–0.068)	0.063 (0.064–0.067)	0.102 (0.089–0.115)	0.159 (0.134–0.176)	0.207 (0.168–0.244)	379
12–19 years	1999–2000	0.158 (0.141–0.178)	0.170 (0.150–0.180)	0.240 (0.210–0.270)	0.350 (0.290–0.420)	0.460 (0.350–0.510)	663
	2001–2002	0.169 (0.156–0.184)	0.160 (0.150–0.180)	0.240 (0.220–0.260)	0.350 (0.320–0.410)	0.460 (0.400–0.500)	762
	2003–2004	0.105 (0.095–0.115)	0.100 (0.090–0.120)	0.150 (0.140–0.160)	0.230 (0.200–0.270)	0.290 (0.250–0.370)	725
	2005–2006	0.092 (0.083–0.101)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.240 (0.200–0.270)	0.280 (0.250–0.320)	701
	2007–2008	0.079 (0.069–0.091)	0.080 (0.070–0.090)	0.130 (0.110–0.140)	0.210 (0.150–0.230)	0.230 (0.210–0.340)	376
	2009–2010	0.063 (0.056–0.071)	0.060 (0.050–0.070)	0.100 (0.090–0.120)	0.180 (0.150–0.210)	0.270 (0.180–0.370)	451
	2011–2012	0.065 (0.057–0.073)	0.065 (0.048–0.081)	0.106 (0.098–0.126)	0.173 (0.137–0.202)	0.218 (0.166–0.283)	390
	2013–2014	0.051 (0.043–0.061)	0.051 (0.041–0.062)	0.088 (0.070–0.112)	0.138 (0.121–0.166)	0.203 (0.152–0.235)	451
	2015–2016	0.059 (0.051–0.068)	0.060 (0.047–0.069)	0.094 (0.080–0.118)	0.160 (0.129–0.207)	0.259 (0.178–0.292)	402

Table 5-12. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
≥20 years	1999–2000	0.123 (0.112–0.137)	0.120 (0.110–0.130)	0.200 (0.180–0.220)	0.310 (0.290–0.350)	0.430 (0.390–0.470)	1,297
	2001–2002	0.128 (0.119–0.136)	0.130 (0.120–0.130)	0.180 (0.170–0.190)	0.250 (0.220–0.300)	0.330 (0.280–0.390)	1,560
	2003–2004	*	0.070 (<LOD–0.080)	0.120 (0.100–0.140)	0.190 (0.170–0.210)	0.270 (0.220–0.320)	1,543
	2005–2006	0.070 (0.064–0.078)	0.070 (0.060–0.080)	0.120 (0.110–0.140)	0.220 (0.180–0.270)	0.320 (0.260–0.420)	1,520
	2007–2008	0.058 (0.054–0.062)	0.060 (0.050–0.060)	0.090 (0.090–0.100)	0.160 (0.130–0.190)	0.240 (0.210–0.270)	1,857
	2009–2010	0.054 (0.051–0.057)	0.050 (0.050–0.050)	0.090 (0.080–0.090)	0.150 (0.140–0.180)	0.220 (0.190–0.270)	2,018
	2011–2012	*	0.044 (<LOD–0.051)	0.076 (0.066–0.087)	0.129 (0.112–0.152)	0.171 (0.158–0.228)	1,715
	2013–2014	0.042 (0.038–0.045)	0.039 (0.033–0.043)	0.071 (0.065–0.079)	0.128 (0.116–0.137)	0.184 (0.161–0.215)	1,811
	2015–2016	0.045 (0.042–0.047)	0.044 (0.040–0.048)	0.077 (0.073–0.080)	0.131 (0.113–0.147)	0.191 (0.161–0.209)	1,794
Gender							
Males	1999–2000	0.143 (0.131–0.157)	0.150 (0.130–0.160)	0.240 (0.220–0.260)	0.350 (0.330–0.390)	0.470 (0.390–0.570)	1,132
	2001–2002	0.145 (0.136–0.154)	0.140 (0.130–0.150)	0.200 (0.190–0.210)	0.310 (0.280–0.330)	0.390 (0.350–0.440)	1,335
	2003–2004	0.095 (0.088–0.103)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.220 (0.200–0.250)	0.320 (0.270–0.350)	1,281
	2005–2006	0.085 (0.076–0.095)	0.080 (0.080–0.090)	0.140 (0.120–0.160)	0.250 (0.210–0.290)	0.350 (0.260–0.460)	1,271
	2007–2008	0.068 (0.062–0.076)	0.070 (0.060–0.070)	0.110 (0.100–0.120)	0.210 (0.170–0.230)	0.280 (0.230–0.340)	1,327
	2009–2010	0.060 (0.055–0.065)	0.060 (0.050–0.070)	0.100 (0.090–0.110)	0.170 (0.150–0.200)	0.250 (0.200–0.290)	1,397
	2011–2012	0.057 (0.052–0.063)	0.052 (0.044–0.061)	0.089 (0.080–0.100)	0.152 (0.124–0.169)	0.196 (0.169–0.259)	1,262
	2013–2014	0.048 (0.044–0.052)	0.046 (0.041–0.051)	0.082 (0.072–0.094)	0.145 (0.129–0.161)	0.213 (0.182–0.230)	1,318
	2015–2016	0.053 (0.049–0.058)	0.053 (0.047–0.058)	0.090 (0.080–0.103)	0.156 (0.137–0.162)	0.209 (0.175–0.248)	1,524
Females	1999–2000	0.122 (0.109–0.137)	0.120 (0.110–0.140)	0.200 (0.180–0.220)	0.300 (0.280–0.340)	0.400 (0.350–0.460)	1,144
	2001–2002	0.125 (0.117–0.133)	0.120 (0.120–0.130)	0.180 (0.160–0.190)	0.240 (0.220–0.280)	0.320 (0.260–0.360)	1,355
	2003–2004	*	<LOD	0.120 (0.090–0.140)	0.180 (0.150–0.220)	0.230 (0.190–0.330)	1,277
	2005–2006	0.063 (0.057–0.071)	0.060 (0.050–0.070)	0.100 (0.090–0.120)	0.180 (0.150–0.230)	0.270 (0.200–0.330)	1,305
	2007–2008	0.055 (0.052–0.058)	0.050 (0.050–0.060)	0.090 (0.080–0.100)	0.130 (0.120–0.150)	0.200 (0.170–0.230)	1,300
	2009–2010	0.052 (0.049–0.056)	0.050 (0.040–0.050)	0.090 (0.080–0.090)	0.150 (0.130–0.170)	0.220 (0.190–0.270)	1,450
	2011–2012	*	0.043 (<LOD–0.049)	0.074 (0.068–0.082)	0.131 (0.122–0.149)	0.182 (0.166–0.218)	1,242
	2013–2014	0.040 (0.036–0.044)	0.036 (0.030–0.043)	0.070 (0.062–0.078)	0.122 (0.105–0.132)	0.169 (0.146–0.200)	1,346
	2015–2016	0.042 (0.039–0.045)	0.042 (0.037–0.045)	0.072 (0.067–0.078)	0.117 (0.107–0.131)	0.178 (0.150–0.205)	1,537

Table 5-12. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	1999–2000	0.132 (0.108–0.161)	0.140 (0.120–0.170)	0.210 (0.180–0.240)	0.300 (0.260–0.390)	0.430 (0.330–0.560)	787
	2001–2002	0.142 (0.130–0.154)	0.130 (0.130–0.150)	0.200 (0.170–0.230)	0.260 (0.240–0.320)	0.360 (0.300–0.400)	683
	2003–2004	0.093 (0.079–0.110)	0.090 (<LOD–0.120)	0.140 (0.120–0.160)	0.190 (0.160–0.260)	0.270 (0.210–0.330)	618
	2005–2006	0.093 (0.082–0.105)	0.090 (0.080–0.100)	0.150 (0.140–0.170)	0.250 (0.210–0.340)	0.470 (0.270–0.850)	652
	2007–2008	0.069 (0.060–0.079)	0.070 (0.060–0.080)	0.110 (0.100–0.120)	0.190 (0.150–0.250)	0.270 (0.220–0.390)	515
	2009–2010	0.063 (0.060–0.067)	0.060 (0.060–0.070)	0.110 (0.090–0.120)	0.170 (0.150–0.200)	0.250 (0.200–0.270)	613
	2011–2012	0.056 (0.051–0.062)	0.053 (0.044–0.062)	0.086 (0.075–0.091)	0.134 (0.110–0.164)	0.174 (0.149–0.261)	317
	2013–2014	0.048 (0.038–0.060)	0.047 (0.033–0.057)	0.082 (0.066–0.106)	0.172 (0.109–0.248)	0.252 (0.170–0.432)	453
	2015–2016	0.057 (0.052–0.062)	0.057 (0.053–0.063)	0.090 (0.084–0.098)	0.139 (0.121–0.165)	0.194 (0.167–0.284)	585
Non-Hispanic blacks	1999–2000	0.175 (0.148–0.207)	0.180 (0.150–0.200)	0.260 (0.230–0.300)	0.400 (0.310–0.490)	0.490 (0.410–0.710)	554
	2001–2002	0.180 (0.164–0.197)	0.170 (0.160–0.190)	0.250 (0.220–0.280)	0.360 (0.320–0.410)	0.460 (0.370–0.530)	667
	2003–2004	0.108 (0.098–0.119)	0.110 (0.100–0.120)	0.160 (0.150–0.190)	0.230 (0.200–0.280)	0.310 (0.250–0.360)	723
	2005–2006	0.088 (0.077–0.100)	0.090 (0.080–0.100)	0.140 (0.130–0.170)	0.210 (0.190–0.250)	0.280 (0.240–0.320)	692
	2007–2008	0.085 (0.079–0.092)	0.080 (0.080–0.090)	0.130 (0.120–0.140)	0.210 (0.180–0.250)	0.290 (0.250–0.370)	589
	2009–2010	0.073 (0.065–0.081)	0.070 (0.060–0.080)	0.120 (0.110–0.140)	0.190 (0.160–0.250)	0.280 (0.220–0.350)	544
	2011–2012	0.070 (0.063–0.079)	0.068 (0.062–0.074)	0.110 (0.096–0.125)	0.182 (0.148–0.229)	0.254 (0.200–0.354)	669
	2013–2014	0.065 (0.056–0.075)	0.066 (0.060–0.070)	0.111 (0.097–0.128)	0.189 (0.146–0.225)	0.245 (0.218–0.303)	581
	2015–2016	0.068 (0.062–0.075)	0.066 (0.057–0.073)	0.110 (0.097–0.127)	0.192 (0.166–0.219)	0.265 (0.211–0.319)	671
Non-Hispanic whites	1999–2000	0.128 (0.115–0.144)	0.130 (0.110–0.140)	0.210 (0.190–0.230)	0.330 (0.280–0.350)	0.400 (0.360–0.500)	768
	2001–2002	0.126 (0.117–0.135)	0.130 (0.120–0.130)	0.180 (0.170–0.190)	0.250 (0.230–0.300)	0.340 (0.310–0.390)	1,132
	2003–2004	*	0.070 (<LOD–0.080)	0.130 (0.110–0.140)	0.190 (0.170–0.210)	0.280 (0.230–0.320)	1,074
	2005–2006	0.069 (0.062–0.077)	0.070 (0.060–0.080)	0.110 (0.100–0.130)	0.210 (0.170–0.260)	0.300 (0.240–0.380)	1,041
	2007–2008	0.057 (0.052–0.063)	0.060 (0.050–0.060)	0.090 (0.080–0.110)	0.150 (0.130–0.200)	0.230 (0.190–0.260)	1,095
	2009–2010	0.053 (0.050–0.057)	0.050 (0.040–0.050)	0.090 (0.080–0.090)	0.160 (0.130–0.190)	0.230 (0.190–0.280)	1,225
	2011–2012	*	0.044 (<LOD–0.049)	0.081 (0.069–0.095)	0.143 (0.118–0.159)	0.180 (0.159–0.231)	820
	2013–2014	0.041 (0.037–0.045)	0.037 (0.032–0.043)	0.071 (0.063–0.079)	0.118 (0.104–0.130)	0.167 (0.143–0.184)	985
	2015–2016	0.044 (0.041–0.047)	0.043 (0.039–0.047)	0.075 (0.068–0.081)	0.129 (0.112–0.144)	0.178 (0.155–0.208)	924
All Hispanics	2011–2012	*	0.046 (<LOD–0.053)	0.079 (0.066–0.088)	0.128 (0.110–0.149)	0.174 (0.149–0.208)	573
	2013–2014	0.047 (0.040–0.055)	0.045 (0.038–0.052)	0.079 (0.069–0.096)	0.155 (0.116–0.218)	0.231 (0.178–0.318)	701
	2015–2016	0.054 (0.050–0.058)	0.053 (0.048–0.058)	0.086 (0.080–0.094)	0.136 (0.117–0.161)	0.205 (0.167–0.264)	982

Table 5-12. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Asians	2011–2012	*	<LOD	0.066 (0.054–0.075)	0.103 (0.075–0.145)	0.145 (0.100–0.194)	353
	2013–2014	*	0.027 (<LOD–0.052)	0.052 (0.045–0.061)	0.080 (0.065–0.098)	0.099 (0.083–0.169)	292
	2015–2016	0.033 (0.028–0.038)	0.053 (0.022–0.039)	0.051 (0.042–0.061)	0.092 (0.062–0.134)	0.139 (0.095–0.208)	332

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2019

Table 5-13. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	0.124 (0.108–0.143)	0.119 (0.102–0.143)	0.185 (0.164–0.214)	0.276 (0.233–0.333)	0.385 (0.333–0.430)	2,276
	2001–2002	0.126 (0.119–0.134)	0.120 (0.115–0.126)	0.173 (0.162–0.188)	0.267 (0.242–0.300)	0.364 (0.320–0.414)	2,689
	2003–2004	*	0.080 (<LOD–0.086)	0.135 (0.119–0.143)	0.208 (0.192–0.230)	0.277 (0.250–0.294)	2,558
	2005–2006	0.072 (0.068–0.077)	0.070 (0.060–0.070)	0.100 (0.100–0.110)	0.160 (0.150–0.190)	0.230 (0.190–0.290)	2,576
	2007–2008	0.064 (0.060–0.068)	0.060 (0.060–0.060)	0.090 (0.080–0.100)	0.140 (0.140–0.160)	0.200 (0.170–0.230)	2,627
	2009–2010	0.060 (0.056–0.064)	0.060 (0.050–0.060)	0.090 (0.080–0.090)	0.140 (0.120–0.160)	0.200 (0.180–0.230)	2,847
	2011–2012	*	0.059 (0.055–0.063)	0.092 (0.085–0.100)	0.152 (0.135–0.171)	0.223 (0.181–0.261)	2,502
	2013–2014	0.050 (0.046–0.055)	0.047 (0.044–0.051)	0.073 (0.068–0.079)	0.114 (0.103–0.127)	0.160 (0.145–0.172)	2,663
	2015–2016	0.053 (0.050–0.056)	0.049 (0.047–0.052)	0.079 (0.071–0.087)	0.124 (0.115–0.137)	0.176 (0.152–0.190)	3,058
Age group							
3-5 years	2015–2016	0.113 (0.103-0.124)	0.108 (0.91-0.117)	0.163 (0.149-0.181)	0.255 (0.220-0.291)	0.328 (0.274-0.425)	485
6–11 years	1999–2000	0.191 (0.147–0.248)	0.185 (0.156–0.220)	0.250 (0.200–0.417)	0.447 (0.271–0.741)	0.741 (0.333–10.30)	316
	2001–2002	0.178 (0.159–0.200)	0.173 (0.150–0.193)	0.228 (0.200–0.272)	0.338 (0.265–0.480)	0.471 (0.313–0.727)	368
	2003–2004	0.116 (0.103–0.130)	0.118 (0.098–0.136)	0.167 (0.146–0.187)	0.256 (0.194–0.317)	0.333 (0.250–0.500)	290
	2005–2006	0.092 (0.081–0.104)	0.090 (0.080–0.110)	0.130 (0.110–0.150)	0.180 (0.150–0.210)	0.220 (0.180–0.270)	355
	2007–2008	0.089 (0.079–0.100)	0.090 (0.070–0.100)	0.120 (0.110–0.140)	0.200 (0.150–0.240)	0.300 (0.200–0.370)	394
	2009–2010	0.094 (0.084–0.106)	0.090 (0.080–0.100)	0.140 (0.120–0.160)	0.200 (0.170–0.250)	0.280 (0.220–0.320)	378
	2011–2012	0.091 (0.081–0.102)	0.091 (0.078–0.100)	0.130 (0.116–0.147)	0.206 (0.153–0.283)	0.308 (0.218–0.340)	398
	2013–2014	0.077 (0.068–0.088)	0.076 (0.067–0.084)	0.114 (0.098–0.133)	0.177 (0.154–0.193)	0.225 (0.191–0.238)	402
	2015–2016	0.086 (0.077–0.096)	0.084 (0.073–0.096)	0.125 (0.114–0137)	0.183 (0.155–0.210)	0.250 (0.196–0.300)	379
12–19 years	1999–2000	0.121 (0.104–0.140)	0.120 (0.095–0.146)	0.176 (0.146–0.207)	0.259 (0.206–0.310)	0.310 (0.228–0.421)	663
	2001–2002	0.121 (0.112–0.131)	0.115 (0.106–0.127)	0.160 (0.138–0.186)	0.224 (0.199–0.245)	0.266 (0.244–0.310)	762
	2003–2004	0.075 (0.068–0.082)	0.068 (0.061–0.077)	0.100 (0.092–0.113)	0.156 (0.126–0.173)	0.193 (0.172–0.255)	725
	2005–2006	0.070 (0.065–0.076)	0.070 (0.060–0.080)	0.100 (0.090–0.110)	0.140 (0.120–0.150)	0.170 (0.150–0.250)	701
	2007–2008	0.062 (0.054–0.070)	0.060 (0.050–0.070)	0.090 (0.070–0.100)	0.120 (0.100–0.160)	0.160 (0.110–0.240)	376
	2009–2010	0.059 (0.053–0.066)	0.060 (0.050–0.060)	0.090 (0.070–0.100)	0.130 (0.110–0.170)	0.180 (0.150–0.220)	451
	2011–2012	0.062 (0.055–0.069)	0.058 (0.051–0.067)	0.085 (0.070–0.106)	0.147 (0.115–0.181)	0.222 (0.122–0.373)	390
	2013–2014	0.046 (0.041–0.053)	0.047 (0.039–0.052)	0.064 (0.057–0.071)	0.103 (0.084–0.115)	0.144 (0.109–0.172)	451
	2015–2016	0.055 (0.049–0.062)	0.050 (0.045–0.059)	0.075 (0.065–0.085)	0.114 (0.096–0.133)	0.148 (0.128–0.200)	402

Table 5-13. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
≥20 years	1999–2000	0.118 (0.104–0.135)	0.111 (0.097–0.135)	0.175 (0.149–0.209)	0.263 (0.227–0.320)	0.352 (0.320–0.391)	1,297
	2001–2002	0.122 (0.115–0.129)	0.115 (0.108–0.121)	0.167 (0.153–0.181)	0.265 (0.241–0.300)	0.364 (0.318–0.405)	1,559
	2003–2004	*	0.079 (<LOD–0.087)	0.135 (0.116–0.145)	0.209 (0.195–0.233)	0.278 (0.250–0.294)	1,543
	2005–2006	0.070 (0.066–0.075)	0.060 (0.060–0.070)	0.100 (0.090–0.110)	0.170 (0.150–0.190)	0.250 (0.190–0.300)	1,520
	2007–2008	0.062 (0.058–0.066)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.200 (0.160–0.240)	1,857
	2009–2010	0.057 (0.053–0.061)	0.050 (0.050–0.060)	0.080 (0.080–0.090)	0.130 (0.120–0.140)	0.190 (0.160–0.220)	2,018
	2011–2012	*	0.056 (<LOD–0.060)	0.088 (0.078–0.097)	0.145 (0.127–0.171)	0.215 (0.179–0.240)	1,714
	2013–2014	0.049 (0.044–0.053)	0.046 (0.043–0.049)	0.070 (0.064–0.076)	0.104 (0.095–0.115)	0.151 (0.130–0.170)	1,810
	2015–2016	0.049 (0.046–0.051)	0.046 (0.043–0.048)	0.070 (0.064–0.078)	0.113 (0.103–0.122)	0.151 (0.130–0.177)	1,792
Gender							
Males	1999–2000	0.112 (0.099–0.127)	0.109 (0.095–0.127)	0.164 (0.146–0.181)	0.226 (0.204–0.268)	0.320 (0.235–0.391)	1,132
	2001–2002	0.114 (0.107–0.123)	0.108 (0.103–0.115)	0.153 (0.138–0.171)	0.228 (0.205–0.250)	0.333 (0.281–0.438)	1,334
	2003–2004	0.080 (0.076–0.084)	0.075 (0.069–0.081)	0.122 (0.111–0.132)	0.192 (0.173–0.209)	0.253 (0.230–0.278)	1,281
	2005–2006	0.070 (0.064–0.077)	0.060 (0.060–0.070)	0.100 (0.090–0.120)	0.160 (0.130–0.220)	0.250 (0.170–0.310)	1,271
	2007–2008	0.061 (0.057–0.066)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.210 (0.160–0.260)	1,327
	2009–2010	0.055 (0.050–0.060)	0.050 (0.050–0.060)	0.080 (0.070–0.100)	0.130 (0.120–0.150)	0.190 (0.160–0.210)	1,397
	2011–2012	0.054 (0.050–0.058)	0.051 (0.048–0.057)	0.078 (0.071–0.089)	0.132 (0.120–0.151)	0.186 (0.161–0.224)	1,261
	2013–2014	0.048 (0.043–0.053)	0.045 (0.040–0.049)	0.068 (0.061–0.076)	0.114 (0.099–0.123)	0.163 (0.145–0.177)	1,317
	2015–2016	0.051 (0.047–0.055)	0.047 (0.043–0.048)	0.076 (0.067–0.089)	0.125 (0.112–0.140)	0.178 (0.151–0.211)	1,524
Females	1999–2000	0.137 (0.117–0.161)	0.131 (0.108–0.164)	0.213 (0.176–0.247)	0.320 (0.263–0.417)	0.429 (0.357–0.485)	1,144
	2001–2002	0.139 (0.131–0.148)	0.132 (0.124–0.140)	0.196 (0.178–0.211)	0.295 (0.267–0.317)	0.371 (0.333–0.444)	1,355
	2003–2004	*	<LOD	0.143 (0.125–0.161)	0.225 (0.188–0.261)	0.288 (0.250–0.333)	1,277
	2005–2006	0.074 (0.070–0.078)	0.070 (0.070–0.070)	0.110 (0.100–0.110)	0.170 (0.150–0.190)	0.220 (0.180–0.300)	1,305
	2007–2008	0.067 (0.062–0.071)	0.060 (0.060–0.070)	0.100 (0.090–0.100)	0.140 (0.130–0.160)	0.200 (0.160–0.230)	1,300
	2009–2010	0.064 (0.060–0.069)	0.060 (0.060–0.070)	0.090 (0.090–0.100)	0.150 (0.130–0.170)	0.220 (0.180–0.260)	1,450
	2011–2012	*	0.066 (<LOD–0.071)	0.104 (0.094–0.112)	0.165 (0.145–0.193)	0.226 (0.183–0.303)	1,241
	2013–2014	0.053 (0.048–0.057)	0.050 (0.046–0.055)	0.077 (0.071–0.084)	0.114 (0.104–0.133)	0.156 (0.145–0.171)	1,346
	2015–2016	0.055 (0.052–0.059)	0.051 (0.048–0.055)	0.081 (0.073–0.090)	0.123 (0.114–0.139)	0.172 (0.144–0.196)	1,534

Table 5-13. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	1999–2000	0.120 (0.107–0.135)	0.114 (0.105–0.129)	0.167 (0.148–0.203)	0.250 (0.209–0.315)	0.333 (0.280–0.357)	787
	2001–2002	0.138 (0.128–0.149)	0.130 (0.117–0.143)	0.182 (0.159–0.203)	0.269 (0.229–0.308)	0.338 (0.308–0.429)	682
	2003–2004	0.086 (0.076–0.098)	0.082 (<LOD–0.092)	0.129 (0.107–0.151)	0.189 (0.154–0.238)	0.238 (0.185–0.321)	618
	2005–2006	0.087 (0.076–0.099)	0.080 (0.070–0.080)	0.120 (0.110–0.130)	0.190 (0.150–0.310)	0.370 (0.200–0.800)	652
	2007–2008	0.069 (0.059–0.081)	0.060 (0.050–0.080)	0.100 (0.080–0.120)	0.160 (0.130–0.180)	0.200 (0.160–0.360)	515
	2009–2010	0.066 (0.063–0.071)	0.060 (0.060–0.060)	0.100 (0.080–0.110)	0.160 (0.130–0.190)	0.240 (0.190–0.280)	613
	2011–2012	0.063 (0.059–0.067)	0.061 (0.057–0.064)	0.089 (0.079–0.100)	0.133 (0.121–0.153)	0.183 (0.150–0.246)	317
	2013–2014	0.055 (0.046–0.066)	0.049 (0.043–0.057)	0.076 (0.063–0.099)	0.138 (0.107–0.172)	0.196 (0.137–0.381)	453
	2015–2016	0.062 (0.057–0.069)	0.056 (0.051–0.062)	0.094 (0.084–0.101)	0.140 (0.126–0.166)	0.224 (0.166–0.275)	584
Non-Hispanic blacks	1999–2000	0.114 (0.099–0.133)	0.112 (0.098–0.130)	0.163 (0.144–0.183)	0.236 (0.195–0.338)	0.343 (0.255–0.425)	554
	2001–2002	0.123 (0.113–0.134)	0.115 (0.106–0.127)	0.163 (0.150–0.181)	0.233 (0.208–0.267)	0.300 (0.248–0.373)	667
	2003–2004	0.078 (0.071–0.085)	0.074 (0.069–0.082)	0.109 (0.096–0.124)	0.170 (0.148–0.192)	0.222 (0.179–0.257)	723
	2005–2006	0.064 (0.058–0.071)	0.060 (0.050–0.070)	0.090 (0.080–0.090)	0.130 (0.120–0.150)	0.190 (0.150–0.220)	692
	2007–2008	0.062 (0.059–0.066)	0.060 (0.050–0.070)	0.090 (0.080–0.090)	0.140 (0.120–0.160)	0.180 (0.160–0.220)	589
	2009–2010	0.058 (0.053–0.063)	0.060 (0.050–0.060)	0.080 (0.070–0.090)	0.130 (0.110–0.160)	0.170 (0.150–0.190)	544
	2011–2012	0.055 (0.049–0.060)	0.052 (0.047–0.058)	0.077 (0.069–0.088)	0.121 (0.104–0.147)	0.175 (0.140–0.232)	669
	2013–2014	0.049 (0.046–0.053)	0.048 (0.044–0.052)	0.068 (0.064–0.073)	0.110 (0.095–0.122)	0.164 (0.133–0.221)	581
	2015–2016	0.054 (0.049–0.060)	0.048 (0.045–0.052)	0.080 (0.068–0.088)	0.136 (0.113–0.179)	0.226 (0.167–0.280)	669
Non-Hispanic whites	1999–2000	0.129 (0.109–0.152)	0.125 (0.102–0.152)	0.195 (0.167–0.225)	0.298 (0.239–0.352)	0.400 (0.333–0.444)	768
	2001–2002	0.127 (0.117–0.138)	0.120 (0.113–0.130)	0.176 (0.159–0.198)	0.280 (0.241–0.317)	0.380 (0.318–0.471)	1,132
	2003–2004	*	0.081 (<LOD–0.089)	0.139 (0.124–0.147)	0.217 (0.200–0.238)	0.286 (0.253–0.333)	1,074
	2005–2006	0.072 (0.068–0.077)	0.070 (0.060–0.070)	0.110 (0.100–0.110)	0.170 (0.150–0.190)	0.230 (0.190–0.280)	1,041
	2007–2008	0.064 (0.060–0.069)	0.060 (0.050–0.070)	0.090 (0.080–0.100)	0.140 (0.140–0.160)	0.210 (0.170–0.230)	1,095
	2009–2010	0.060 (0.055–0.065)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.120–0.170)	0.200 (0.170–0.250)	1,225
	2011–2012	*	0.060 (<LOD–0.067)	0.097 (0.088–0.108)	0.161 (0.135–0.183)	0.224 (0.181–0.273)	818
	2013–2014	0.050 (0.044–0.056)	0.047 (0.042–0.053)	0.075 (0.068–0.081)	0.110 (0.098–0.127)	0.156 (0.133–0.171)	984
	2015–2016	0.052 (0.048–0.055)	0.049 (0.046–0.053)	0.077 (0.068–0.089)	0.136 (0.106–0.132)	0.160 (0.138–0.180)	924
All Hispanics	2011–2012	*	0.058 (<LOD–0.065)	0.085 (0.073–0.097)	0.132 (0.113–0.161)	0.181 (0.153–0.214)	573
	2013–2014	0.052 (0.044–0.056)	0.047 (0.043–0.054)	0.076 (0.065–0.089)	0.137 (0.107–0.164)	0.196 (0.143–0.326)	701
	2015–2016	0.061 (0.048–0.055)	0.055 (0.049–0.060)	0.092 (0.085–0.100)	0.143 (0.132–0.162)	0.246 (0.183–0.300)	981

Table 5-13. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Asians	2011–2012	*	<LOD	0.087 (0.072–0.107)	0.153 (0.132–0.177)	0.215 (0.171–0.290)	353
	2013–2014	*	0.047 (<LOD–0.050)	0.067 (0.060–0.077)	0.114 (0.087–0.145)	0.160 (0.133–0.201)	292
	2015–2016	0.045 (0.039–0.051)	0.041 (0.037–0.047)	0.067 (0.065–0.080)	0.114 (0.087–0.144)	0.167 (0.125–0.223)	332

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2019

study analyzing antimony concentrations in washed hair samples from 234 healthy individuals reported a geometric mean concentration and standard deviation of 0.078 and 2.5 ppm, respectively. No significant differences between different sexes or age groups were noted (Ohmori et al. 1981).

In another Japanese study, hair and nail samples taken from workers at an antimony refinery, nearby residents, and a control group were analyzed before and after washing with a nonionic, surface-active agent in an ultrasonic cleaner (Katayama and Ishide 1987). The respective concentrations of antimony in the nails of the three groups were 730, 2.46, and 0.19 ppm before washing and 230, 0.63, and 0.09 ppm after washing. The concentrations of antimony in the hair of workers before and after washing were 222 and 196 ppm, respectively. The concentrations of antimony in the hair of control subjects before and after washing were 0.21 and 0.15 ppm, respectively. Nail samples from 71 Americans contained an average of 0.41 ppm of antimony. Averages for residents of four other countries ranged from 0.28 to 0.70 ppm (Takagi et al. 1988).

The NHANES 1999–2016 reported antimony levels in urine (see Tables 5-12 and 5-13) for children in different age groups (CDC 2019). Infant urinary antimony levels reported in the scientific literature are similar to those reported for young children in Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2019). Antimony levels >1 µg/L were found in 4% of 126 term infants; 7% had levels <0.02 µg/L and 90.5% had levels <0.5 µg/L (Dezateux et al. 1997). Higher levels of antimony were found in postmortem liver and serum samples from infants who died as a result of sudden infant death syndrome (Cullen et al. 1998; Jenkins et al. 1998). Mean serum antimony concentrations ranged from 0.16 to 0.18 µg/L for 100 healthy infants, 2–56 weeks old. Urinary antimony concentrations were not detected in 5% of the infants, the median urinary antimony concentrations were 0.42 ng/mg creatinine, and 95% of the infants had antimony concentrations <2.6 ng/mg creatinine.

Several studies have evaluated the factors that contribute to antimony body burden. A study of Norwegian never-pregnant women found that increasing age (25–40 versus 18–24 years), an omnivore diet (compared to a vegetarian diet), and tobacco use were associated with higher serum antimony levels (Fløtre et al. 2017). A comparison of serum antimony levels in professional athletes and sedentary males found significantly higher serum antimony levels among the athletes (Maynar et al. 2017). When the athletes were divided into groups on whether they participated in aerobic (long distance runners), anaerobic (judo and speed athlethes), or aerobic-anaerobic (soccer players) sports, serum antimony levels in the aerobic athlete group did not differ from the sedentary group. The investigators suggested that the difference between the findings in aerobic athletes and anaerobic athletes may be due to the high levels of

antimony in muscles and because anaerobic athletes have a greater muscle volume. A study of French children 3–6 years of age found that the diet accounted for more 77% of total antimony exposure (Glorennec et al 2016).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Elevated urinary antimony levels were reported in workers exposed to airborne antimony (Bailly et al. 1991; Iavicoli et al. 2002; Kentner et al. 1995; Liao et al. 2004; Ludersdorf et al. 1987). A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 373,460 workers were potentially exposed to antimony (molecular formula unknown) in the United States in 1981–1983 (NIOSH 1989). An estimated 226,645 workers were exposed to antimony trioxide, antimony sulfide, antimony oxide, antimony pentoxide, antimony dialkyldithiocarbamate, and other antimony compounds. The total estimated number of workers exposed to antimony and all of its compounds was 486,347. These estimates are preliminary since all of the data for trade-name products that may contain antimony were not analyzed. The NOES was based on field surveys of 4,490 facilities. It was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons are employed in all standard industrial codes (SIC) except mining and agriculture. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace. EPA states that the NOES figures substantially overestimate occupational exposure to antimony and compounds (EPA 1983).

Reported urinary levels of antimony were high in occupationally exposed individuals compared to levels in control subjects ranging from 0.18–2.16 µg/L. Levels ranged from 0.08 to 32.6 µg/L in the urine of refinery workers, from 0.1 to 36.1 µg/L in chemical manufacturers, and from 1.5 to 149.2 µg/L in battery manufacturers. The authors specified that the levels of antimony were 5 times higher from battery workers than other workers. Battery manufacturers were likely exposed to stibine (SbH_3) during the charging process of batteries (Smith et al. 1995).

Concentrations of antimony were examined in the urine of workers at the Punchancavi site in Chile. Concentrations of total antimony and Sb(V) were 6–6.3 and 2.4–6.2 µg/L, respectively. Urine sample analysis determined that most samples had concentrations of total antimony and Sb(V) that were below the limit of detection. No Sb(III) was found in the samples (Quiroz et al. 2011).

A study of residents living near an electronic waste recycling facility in China found significantly higher hair antimony levels, as compared to residents in another area of China (160.78 ng/g compared to 61.74 ng/g) (Huang et al. 2015). The highest levels were found in the residents that participated in electronic waste recycling activities.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of antimony is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of antimony.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

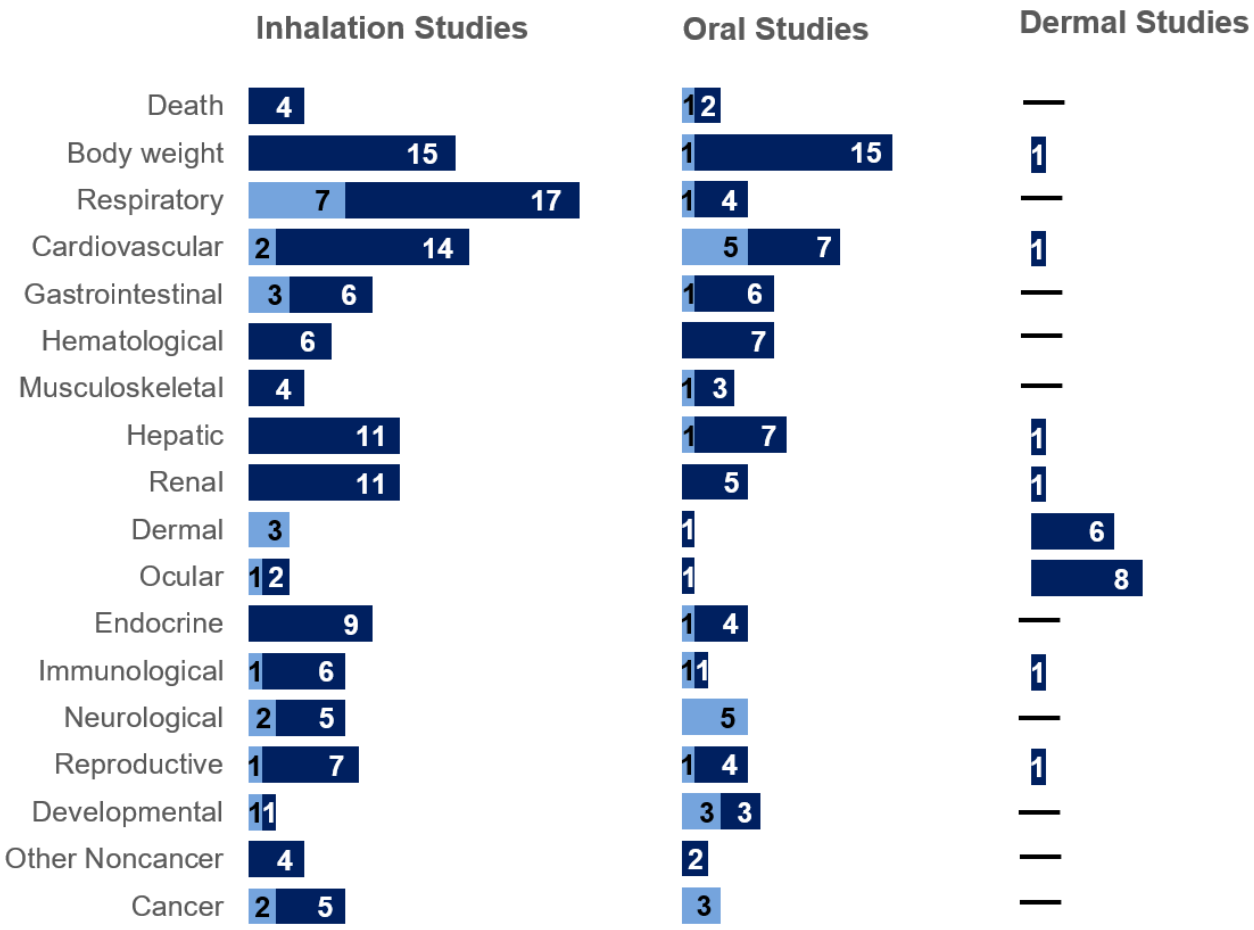
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to antimony that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of antimony. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As summarized in Figure 6-1, there are data available on the health effects of antimony in humans and laboratory animals following inhalation, oral, or dermal exposure. Body weight, respiratory tract, and cardiovascular system were the most studied endpoints in animal toxicology studies.

The epidemiological database consists of occupational exposure, accidental oral exposure, general population exposure, and experimental studies. The inhalation data consist of several reports of workers exposed to inorganic forms of antimony. However, most of these studies are incomplete because the workers were exposed to a variety of compounds or the exposure level was not reported. One oral study involving accidental drinking of lemonade contaminated with potassium antimony tartrate was located. Other studies are population-based studies examining the relationship between urinary antimony levels and health effects. The dermal data on humans are limited to a study in which antimony was applied to the skin of volunteers and occupational exposure studies involving dermal exposure to airborne antimony.

Figure 6-1. Summary of Existing Health Effects Studies on Antimony By Route and Endpoint*

Potential body weight, respiratory, and cardiovascular effects were the most studied endpoints
The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

As compared to the human data, more complete information on the systemic health effects of antimony in animals was located. Inhalation studies predominantly evaluated the toxicity of antimony trioxide, although some studies were available for stibine, antimony trisulfide, and antimony ore. One inhalation study evaluated the reproductive and developmental toxicity of antimony. Several studies that examined the toxicity of metallic antimony, antimony trioxide, antimony trichloride, and potassium antimony tartrate via oral exposure were located. Sensitive measurements of cardiovascular toxicity were not examined in most of these studies. One developmental toxicity study in rats was located; internal examination of pups was not performed. The acute and intermediate toxicity of dermally applied antimony trioxide, antimony oxide, and antimony thioantimonate has been examined. However, the available studies did not examine the systemic toxicity of antimony; they were designed to assess the dermal and/or ocular toxicity of antimony.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. Information on the target organs of acute exposure in humans to antimony is limited to a report of gastrointestinal symptoms in workers acutely exposed to airborne antimony (Taylor 1966). Animal studies have shown that the respiratory tract and heart are the primary targets following inhalation exposure to antimony (Brieger et al. 1954; NIOSH 1979; NTP 2016); there are also limited data suggesting that the liver and kidney are also targets of antimony toxicity (Brieger et al. 1954). An acute inhalation MRL based on respiratory effects in mice (NTP 2016) was derived. The gastrointestinal tract appears to be a target in humans and animals following oral exposure to antimony. This is based on a report of workers who accidentally drank lemonade contaminated with antimony potassium tartrate (Dunn 1928), a dog study reporting vomiting after ingestion of antimony potassium tartrate (Houpt et al. 1984), and a mouse study reporting forestomach ulceration (NTP 1992). Results of the mouse study also suggest that the liver may be a target of antimony toxicity. An acute oral MRL based on the forestomach and liver effects observed in mice was derived. Additional acute-duration studies by the inhalation and oral routes would provide information on differences in the potency of various antimony compounds.

Intermediate-Duration MRLs. No reports of health effects in humans following intermediate-duration inhalation exposure were located. Animal data suggest that the heart and respiratory tract are the likely targets of antimony toxicity following inhalation exposure (Brieger et al. 1954; Newton et al. 1994). Developmental and reproductive effects have also been reported in animals (Belyaeva 1967). The database was adequate for derivation of an intermediate-duration inhalation MRL; however, the resulting value was slightly higher than the acute-duration MRL and the acute MRL was adopted for an intermediate-duration MRL.

There is no information on human health effects following intermediate-duration oral exposure to antimony. Several studies in rats have evaluated the toxicity of antimony following oral exposure (Angrisani et al. 1988; Hext et al. 1999; Poon et al. 1998; Rossi et al. 1987; Sunagawa 1981). These studies have investigated the toxicity of several trivalent antimony compounds (antimony trichloride, antimony potassium tartrate, and antimony trioxide) and metallic antimony and found differences in effect levels that may be related to solubility and absorption efficiency. The most sensitive effects were decreases in blood glucose levels, alterations in red blood cell counts, hepatic alterations, and developmental toxicity. The intermediate-duration oral database was considered adequate for derivation of an MRL. Additional studies examining EKGs would increase the confidence in this MRL, since myocardial damage is a suspected human health effect but has not been adequately assessed in oral exposure studies.

Chronic-Duration MRLs. There are several occupational exposure studies that indicate that the targets appear to be the respiratory tract, heart, and skin following chronic-duration exposure (Brieger et al. 1954; Cooper et al. 1968; Potkonjak and Pavlovich 1983). Animal studies provide strong evidence that the respiratory tract is the primary target of antimony toxicity (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983). Most of the studies tested antimony trioxide, and studies evaluating antimony ore (Groth et al. 1986) or antimony trisulfide (Gross et al. 1952) reported lung effects at the lowest concentration tested; therefore, they are not useful for comparing the relative toxicity of various antimony compounds. Chronic animal studies were considered adequate for deriving a chronic-duration inhalation MRL.

A number of epidemiology studies have evaluated the potential toxicity of environmental exposure to antimony using urinary antimony levels as a dosimetric; these studies are not adequate for establishing causality. Data on chronic oral toxicity in laboratory animals are limited to two studies involving lifetime exposure to antimony potassium tartrate (Kanisawa and Schroeder 1969; Schroeder et al. 1970). Both

studies only tested one concentration and examined a limited number of endpoints. Decreases in survival were observed in both studies, and they were not considered suitable for derivation of a chronic-duration oral MRL. Well-designed oral experiments, using several exposure levels and measuring all sensitive toxicological endpoints, would provide information on the health effects associated with long-term exposure to antimony.

Health Effects. The toxicity of antimony has been evaluated in a number of inhalation and oral studies in laboratory animals. Most of these studies involved exposure to trivalent antimony, a small number of studies evaluated stibine (inhalation exposure) or metallic antimony (oral exposure). No inhalation or oral studies have evaluated the toxicity of pentavalent antimony compounds. Environmental monitoring data suggest that pentavalent antimony compounds is the predominant form in water. Studies on pentavalent antimony would be useful to evaluate whether there are differences between pentavalent and trivalent antimony toxicity. Studies are also needed to evaluate the differences between trivalent antimony compounds. Solubility is likely to influence the effect level, but there are inadequate data that compare target tissues or effect levels. Additionally, there are limited data on the mechanisms of toxicity. Mechanistic studies would provide valuable information to support the identification of critical targets of toxicity, extrapolation of effects from animals to humans, and comparison of the toxicity of different antimony compounds.

Immunological. There is limited information on the immunotoxicity of antimony. Two general population studies found alterations in immunoglobin levels (Kim et al. 1999; Wu and Chen 2017). Inhalation studies in laboratory animals have reported hyperplasia in the bronchial and mediastinal lymph nodes following chronic exposure in rats and mice (Newton et al. 1994; NTP 2016). An oral study found histological alterations in the thymus of rats exposed to antimony potassium tartrate (Poon et al. 1998). A skin sensitization study concluded that dermal exposure to antimony sulfide did not result in sensitization (Horton et al. 1986). No other studies have evaluated immune function; additional functional studies would be useful for evaluating the potential immunotoxicity of antimony in humans.

Neurological. The potential neurotoxicity of antimony has not been investigated in humans or animals following inhalation, oral, or dermal exposure. An occupational exposure study (Renes 1953) reported some neurological effects; however, the lack of a control group and co-exposure to other compounds including arsenic limits establishing causality with antimony. Animal studies have not found histological alterations in the brain following inhalation or oral exposure (Groth et

al. 1986; Hext et al. 1999; NTP 1992, 2016; Poon et al. 1998; Watt 1983). A study in which mice were repeatedly administered antimony potassium tartrate via intraperitoneal injections reported degenerative changes in the anterior horn cells of the lumbar spine and sciatic nerve edema (Mansour and Reese 1965). Although this effect has not been observed by other routes of exposure, this endpoint has not been well studied. Sensitive tests of neurophysiological function may detect early signs of neurotoxicity following inhalation, oral, or dermal exposure to antimony.

Reproductive. Women exposed to antimony in the workplace have reported menstrual disturbances and a higher incidence of spontaneous abortions compared with nonexposed workers (Belyaeva 1967). From this report, it is unclear what the exposure level was, whether the women were exposed also to other compounds, and whether the controls had comparable jobs. Reproductive effects (failure to conceive, uterine metaplasia) have been observed in rats exposed to airborne antimony (Belyaeva 1967). Data on the reproductive toxicity of antimony following oral exposure are limited to a series of studies finding no alterations in sperm parameters in rats and mice exposed to antimony trioxide or antimony potassium tartrate (Omura et al. 2002). Well-designed studies to assess potential effects of antimony on reproductive performance would provide information on possible reproductive effects that might be relevant to humans.

Developmental. An increased number of spontaneous abortions was observed in women exposed to antimony in the workplace (Belyaeva 1967). However, there are several limitations to this study, as discussed above in the reproductive toxicity section. No overt developmental effects were observed in the offspring of these women. Two other epidemiology studies did not find associations between antimony levels in drinking water and the prevalence of neural tube defects (Longerich et al. 1991) and or between umbilical cord antimony levels and adverse pregnancy outcomes (Zheng et al. 2014). A developmental toxicity study in rats found decreases in pup growth and no alterations in the occurrence of structural abnormalities resulting from gestational exposure to antimony potassium tartrate in drinking water (Rossi et al. 1987). Additionally, two studies examining the effect of antimony on the development of the cardiovascular system found alterations in vasomotor reactivity in the offspring (Angrisani et al. 1988; Rossi et al. 1987); however, since this endpoint was not examined in adults, it is difficult to determine whether the effects are developmental in nature. Additional studies examining the potential of antimony to affect the development of the cardiovascular system would be useful.

Cancer. Two occupational exposure studies have found increases in the risk of lung cancer in workers (Jones 1994; Schnorr et al. 1995); a general population study did not find associations between cancer deaths or self-reported cancers (Guo et al. 2016). Evidence for the carcinogenicity of inhaled antimony in animals is mixed. Two 1-year studies reported lung tumors in rats exposed to relatively low levels of antimony trioxide (Groth et al. 1986; Watt 1983). A third study using similar exposure levels and exposure durations did not find evidence of carcinogenicity (Newton et al. 1994). Two-year studies conducted by NTP (2016), found some evidence of carcinogenic activity in male and female rats and clear evidence of carcinogenic activity in male and female mice (NTP 2016). The oral cancer data in animals are limited to studies that used very low levels of antimony (Kanisawa and Schroeder 1969; Schroeder et al. 1970). No dermal cancer studies in animals were located; however, an inhalation study found an increase in squamous cell carcinoma of the skin, which may have been related to exposure to antimony trioxide (NTP 2016). Oral and dermal studies in rodents using several exposure levels would provide useful information because prolonged exposure to antimony in humans may occur.

Epidemiological and Human Dosimetry Studies. There are several epidemiological occupational exposure studies have evaluated the toxicity of inhaled antimony. However, interpretation of these studies are limited due to inadequate reporting of exposure level and/or particle size information, many studies did not include control groups, and/or the workers were often exposed to a variety of other compounds. Several studies have used NHANES data sets to examine associations between urinary antimony levels and health effects; these studies are not suitable for establishing causality. Epidemiological studies, including workplace monitoring programs, would be useful in order to determine the effects of long-term exposure in humans, with particular attention paid to cardiovascular and respiratory effects.

Biomarkers of Exposure and Effect.

Exposure. Antimony levels can be measured in blood, urine, feces, and hair, and background urinary levels of antimony have been established in the general U.S. population (CDC 2019). Antimony levels in blood, urine, and feces have been shown to increase in response to increased antimony exposure (Cooper et al. 1968; Edel et al. 1983; Felicetti et al. 1974a, 1974b; Gerber et al. 1982; Goodwin and Page 1943; Ludersdorf et al. 1987; Rees et al. 1980). Studies that quantified the relationship between blood and/or urinary levels and airborne antimony concentrations or antimony intake would provide valuable information for screening.

Effect. No antimony-specific biomarkers of effects have been identified. Future studies on the toxicity of antimony should use several antimony exposure levels; this may lead to the identification of subtle biochemical or physiological biomarkers of effects.

Absorption, Distribution, Metabolism, and Excretion. There is some information on the toxicokinetic properties of antimony following oral or inhalation exposure in humans and animals. However, there is limited comparative information on the absorption, distribution, and excretion of different antimony compounds. Furthermore, the site and mechanism of antimony absorption from the gastrointestinal tract have not been elucidated. The influence of nutritional factors as well as the presence of food in the gastrointestinal tract on absorption are not known. Information on the absorption, distribution, and excretion of antimony following dermal application is not known. In addition, a study on the effect of oxidation state on the cellular uptake of antimony and the effect of water solubility of an antimony compound on lung retention/absorption would provide useful information on the toxicity of different antimony compounds.

Comparative Toxicokinetics. Species differences in the toxicokinetics of antimony have been identified (Ainsworth et al. 1990; Felicetti et al. 1974a; Gross et al. 1955; Thomas et al. 1973). However, the absorption, distribution, and excretion of antimony following oral or inhalation exposure in humans is not known. Thus, it is not possible to determine which animal species is the best model for assessing the toxicity of antimony. Information on the toxicokinetic properties of antimony in humans would be useful.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No studies have examined the potential differences in antimony toxicity between adults and children. A toxicokinetic study comparing the distribution and elimination of intramuscularly administered pentavalent antimony found differences in serum antimony levels and elimination half-times between children and adults (Cruz et al. 2007). Toxicity and toxicokinetic studies involving inhalation and oral exposure to mature and young animals would provide valuable information for determining whether children are more susceptible to antimony toxicity.

Physical and Chemical Properties. For inorganic salts, the solubility product coupled with stability constants for the ionic species in solution are the factors determining how much of the compound goes into solution; the solubility in terms of the number of milligrams of the parent compound in solution, as used for organic compounds, is not meaningful. All of the solubility products and stability constants for antimony and its compounds, required for determining the antimony species in natural water and their concentrations, are not available. Other physical and chemical properties in Table 4-2 for which there are no data are generally not well defined for antimony and its compounds or are not useful in determining their environmental fate.

Production, Import/Export, Use, Release, and Disposal. Information on the production, import, and use of antimony and antimony trioxide is readily available. However, information on the production, import, and use patterns of other antimony compounds is not available, and is needed to assess human exposure to these compounds. Except for the recycling of batteries, little information is available concerning the disposal of antimony and its compounds. More detailed information regarding the form of antimony that is disposed of and the disposal methods is necessary to assess the potential exposure to these compounds.

Environmental Fate. In assessing human exposure, the form (valence state, compound, adsorption, coprecipitation, particle size) of antimony and its availability must be considered. This information is site specific and is not always available in the literature.

Bioavailability from Environmental Media. Although there is no information on the absorption efficiency of antimony from environmental media in humans, there is evidence in animals that it is absorbed. The vegetation and soils at sites near antimony smelters are heavily contaminated with antimony. Elevated levels of antimony in various tissues were observed in animals living near the smelter (Ainsworth et al. 1990). An animal study designed to measure the rate of absorption of antimony from environmental media would be useful in assessing the toxicological significance of levels of antimony in the air and soil near hazardous waste sites.

Food Chain Bioaccumulation. Studies indicate that phytoremediation is possible with accumulation and uptake of antimony in plants. Studies on fish and aquatic organisms indicate that the bioconcentration of antimony is low; however, the studies are older (EPA 1979; EPA 1980; Maher 1986). Newer studies on the bioconcentration of antimony in fish and biomagnification in higher trophic levels of animals are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of antimony in contaminated media at hazardous waste sites are needed so that the information obtained on levels of antimony in the environment can be used in combination with the known body burden of antimony to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Levels of antimony in the water, soil, and sediment are dependent on the site. Levels of antimony in the air in Japan were found to be highest from brake abrasion dust (Iijima et al. 2009). Concentrations of antimony in water were higher near ore and mining sites. Levels of antimony in the soil and sediment were dependent on the distance from the source of contamination; higher levels were found for soil depths of 0–5 cm (near the surface) and in sediment found upstream (near the site) (Filella et al. 2009b; Migon and Mori 1999).

Exposure Levels in Humans. Antimony has been detected in urine, blood, hair, and nails in individuals exposed to background levels of antimony. A NOES was conducted; however, the data were from 1981–1983 (NIOSH 1989). This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Monitoring studies are needed for infants and young children particularly since there is the potential for exposure from clothing and household items treated with antimony containing flame retardants.

6.3 ONGOING STUDIES

No ongoing studies examining the toxicity, toxicokinetics or environmental fate of antimony were identified in the National Institute of Health (NIH) RePORTER (2019) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding antimony in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for antimony.

Table 7-1. Regulations and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
	Air		
EPA	RfC		IRIS 1995
	Antimony trioxide	$2x10^{-4}$ mg/m^3 [a]	
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories (antimony)		EPA 2018a
	1-Day health advisory (10-kg child)	0.01 mg/L	
	10-Day health advisory (10-kg child)	0.01 mg/L	
	DWEL	0.01 mg/L	
	Lifetime health advisory	0.006 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL (antimony)	0.006 mg/L	
	RfD (antimony)	$4x10^{-4}$ mg/kg/day[b]	IRIS 1987
WHO	Drinking water quality guidelines (antimony and compounds)		WHO 2017
	Guideline value	0.02 mg/L	
	TDI	6 µg/kg body weight	
FDA	Substances added to food	Not listed[c]	FDA 2018
	Allowable level for antimony in bottled water	0.006 mg/L	FDA 2017
	Cancer		
HHS	Carcinogenicity classification (antimony trioxide)	Reasonably anticipated to be a human carcinogen	NTP 2018
EPA	Carcinogenicity classification	No data	IRIS 1987, 1995

Table 7-1. Regulations and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
IARC	Carcinogenicity classification		IARC 1989
	Antimony trioxide	Group 2B[d]	
	Antimony trisulfide	Group 3[e]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction (antimony and compounds, as Sb)	0.5 mg/m^3	OSHA 2018a, 2018b, 2018c
NIOSH	REL (up to 10-hour TWA)		
	Antimony and compounds (as Sb)	0.5 mg/m^3	NIOSH 2018a
	Stibine	0.1 ppm	NIOSH 2018b
	IDLH		
	Antimony compounds (as Sb)	50 mg/m^3	NIOSH 1994a
	Stibine	5 ppm	NIOSH 1994b
	Emergency Criteria		
EPA	AEGLs-air (stibine)		EPA 2016b
	AEGL-1[f]		
	10-minute	NR[g]	
	30-minute	NR[g]	
	60-minute	NR[g]	
	4-hour	NR[g]	
	8-hour	NR[g]	
	AEGL-2[f]		
	10-minute	4.2 ppm	
	30-minute	2.9 ppm	
	60-minute	1.5 ppm	
	4-hour	0.36 ppm	
	8-hour	0.18 ppm	
	AEGL-3[f]		
	10-minute	28 ppm	
	30-minute	19 ppm	
	60-minute	9.6 ppm	
	4-hour	2.4 ppm	
	8-hour	1.2 ppm	
DOE	PACs-air		DOE 2018b
	PAC-1[h]		
	Antimony	0.5 mg/m^3	
	Antimony pentasulfide	2.5 mg/m^3	
	Antimony potassium tartrate	1.7 mg/m^3	
	Antimony trichloride	0.94 mg/m^3	
	Antimony trioxide	0.6 mg/m^3	
	Stibine	0.14 ppm	

Table 7-1. Regulations and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
	PAC-2[h]		
	Antimony	0.5 mg/m^3	
	Antimony pentasulfide	22 mg/m^3	
	Antimony potassium tartrate	1.7 mg/m^3	
	Antimony trichloride	0.94 mg/m^3	
	Antimony trioxide	0.6 mg/m^3	
	Stibine	1.5 ppm	
	PAC-3[h]		
	Antimony	80 mg/m^3	
	Antimony pentasulfide	130 mg/m^3	
	Antimony potassium tartrate	220 mg/m^3	
	Antimony trichloride	150 mg/m^3	
	Antimony trioxide	96 mg/m^3	
	Stibine	9.6 ppm	

[a]The RfC is based on a calculated BMC10(HEC) of 0.074 mg/cu^3 for pulmonary toxicity and chronic interstitial inflammation in rats.
[b]The RfD is based on a LOAEL of 0.35 mg/kg/day for effects on longevity, blood glucose, and cholesterol in rats.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Group 2B: possibly carcinogenic to humans.
[e]Group 3: not classifiable as to its carcinogenicity to humans.
[f]Definitions of AEGL terminology are available from EPA (2018b).
[g]NR = not recommended due to insufficient data.
[h]Definitions of PAC terminology are available from DOE (2018a).

AEGL = acute exposure guideline levels; BMC = benchmark concentration; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HEC = human equivalent concentration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint Expert Committee on Food Additives; LOAEL = lowest-observed-adverse-effect level; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TDI = tolerable daily intake; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 0.001 mg Sb/m^3
Critical Effect: Squamous metaplasia of the epiglottis
Reference: NTP 2016
Point of Departure: $BMCL_{10}$ of 0.94 mg Sb/m^3
Uncertainty Factor: 30
LSE Graph Key: 3
Species: Mouse

MRL Summary: An acute-duration inhalation MRL of 0.001 mg Sb/m^3 was derived for antimony based on an increased incidence of squamous metaplasia of the epiglottis observed in mice exposed to antimony trioxide for 17 days (NTP 2016). The MRL is based on a $BMCL_{10}$ of 0.94 mg Sb/m^3 (human equivalent $BMCL_{10}$ of 0.035 mg Sb/m^3) and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: No human studies have evaluated the acute inhalation toxicity of antimony. In laboratory animals, the acute toxicity has been evaluated for stibine, antimony trisulfide, and antimony trioxide. These studies clearly identify the respiratory tract as one of the most sensitive targets of antimony toxicity (Brieger et al. 1954; NIOSH 1979; NTP 2016). A 30-minute exposure to 1,395 mg Sb/m^3 as stibine resulted in pulmonary edema and congestion and death in rats and guinea pigs (NIOSH 1979). Chronic lung inflammation was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (7 hours/day) and in rats exposed to 25 mg Sb/m^3 as antimony trioxide for 12 exposures over a 16-day period (6 hours/day) (NTP 2016). NTP (2016) also found squamous metaplasia in the epiglottis of rats and mice exposed to 25 or 12 mg Sb/m^3, respectively. The primary extrarespiratory effects also observed following acute exposure were degenerative changes in the heart and altered EKGs in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide.

Selection of the Principal Study: The Brieger et al. (1954) and NTP (2016) studies were considered for derivation of an acute-duration inhalation MRL. Although the rats and mice in the NTP (2016) study were exposed to antimony trioxide over a 16- or 17-day period, the animals were only exposed for 12 or 13 times and the study was considered to be more reflective of effects associated with acute-duration exposure than intermediate-duration exposure. Potential points of departure (PODs) were calculated for both studies (see Selection of the POD section). The lowest POD was identified for the NTP (2016) mouse study, which was selected as the principal study.

Summary of the Principal Study:

NTP. 2016. Toxicology and carcinogenicity studies of antimony trioxide (CAS No. 1309-64-4) in Wistar HAN [Crl:WI (Han)] rats and B6C3F1/N mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC. NTP TR 590. Draft for Peer Review.

Groups of five male and five female B6C3F1/N mice were exposed to 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 antimony trioxide (0, 3.1, 6.3, 12, 25, and 50 mg Sb/m^3) 6 hours/day, 5 days/week for 13 exposures in a 17-day period. An additional group of five female mice was similarly exposed and held for a 28-day

recovery period. The actual concentrations were 3.71, 7.43, 14.7, 30.2, and 59.4 mg Sb_2O_3/m^3. The MMADs (geometric standard deviations) for the particles were 1.4 (1.9), 1.3 (1.9), 1.5 (1.9), 1.4 (1.9), and 1.4 (1.9) μm for the 3.1, 6.3, 12, 25, and 50 mg Sb/m^3 concentrations, respectively. The following parameters were used to assess toxicity: twice daily observations; body weights on days 1, 6, and 13, and at termination; organ weights (kidney, liver, lung, testis, thymus); and histopathological examination in the control and 50 mg Sb/m^3 group (histopathological examinations of the larynx, lung, lymph nodes, nose, pharynx, and trachea were conducted to a no-effect level). In the animals allowed to recover, antimony levels were measured in blood samples collected at the end of the exposure and recovery periods and in the lungs.

Although the mice were exposed to antimony trioxide over a 17-day period, the animals were only exposed for 13 times and the study was considered to be more reflective of effects associated with acute-duration exposure than intermediate-duration exposure.

No deaths, clinical findings, or alterations in body weight gain were observed. Significant increases in absolute lung weights were observed in males at ≥6.3 mg Sb/m^3 and in females at ≥12 mg Sb/m^3; increases in relative lung weights were observed in males at 50 mg Sb/m^3 and in females at ≥3.1 mg Sb/m^3. Minimal to mild squamous metaplasia was observed in the epiglottis epithelium at ≥25 mg Sb/m^3; the incidences were 0/10 in controls and 2/10, 4/9, 10/10, and 10/10 in the 6.3, 12, 25, and 50 mg Sb/m^3 groups, respectively. Increases in the presence of foreign body (presumably antimony trioxide) were observed in the lungs of mice exposed to ≥3.1 mg Sb/m^3. No concentration-related alterations in lung clearance were observed. The clearance half-times ranged from 47 to 62 days.

Selection of the Point of Departure for the MRL: The MRL is based on a $BMCL_{10}$ of 0.94 mg Sb/m^3 for squamous metaplasia of the epiglottis in male and female mice.

Several endpoints were considered for derivation of an acute-duration inhalation MRL for antimony: altered EKGs and degenerative changes in the heart in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide (Brieger et al. 1954), lung inflammation in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide (Brieger et al. 1954), squamous metaplasia of the epiglottis in male and female rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), chronic lung inflammation in rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), and squamous metaplasia of the epiglottis in male and female mice exposed to ≥12 mg Sb/m^3 as antimony trioxide (NTP 2016).

For the NTP (2016) study, the incidence data (Table A-1) for squamous metaplasia in rats and mice were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS; version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all lesion types, a BMR of 10% was used. Since the response level for chronic inflammation was the same for all non-control concentrations (see Table A-1), BMD modeling was not conducted for this endpoint and the NOAEL was used as the POD. The model predictions for the epiglottal squamous metaplasia for rats and mice are presented in Tables A-2 and A-3 and the fits of the selected models are presented in Figures A-1 and A-2. The Brieger et al. (1954) study only tested one concentration of antimony trisulfide, and was not considered suitable for BMD modeling; the LOAEL of 19.9 mg Sb/m^3 for lung and cardiovascular effects was considered the POD for this study.

Table A-1. Incidence of Respiratory Tract Effects in Male and Female Rats and Mice Exposed to Antimony Trioxide[a]

	Concentrations (mg Sb/m^3)					
Effect	0	3.1	6.3	12	25	50
Rats						
Squamous metaplasia of epiglottis	0/10	–[b]	–[b]	1/10	4/9[c]	5/10[c]
Chronic lung inflammation	0/10	0/10	0/10	0/10	10/10[c]	10/10[b]
Mice						
Squamous metaplasia of epiglottis (male and female)	0/10	–[d]	2/10	4/9[c]	10/10[c]	10/10[c]

[a]Male and female incidences were combined.
[b]Incidence in the female rats was 1/5; males were not examined at these concentrations.
[c]Significantly different from controls.
[d]Incidence in the female mice was 2/5; males were not examined at this concentration.

Source: NTP 2016

Table A-2. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Rats (Combined) Exposed to Antimony Trioxide (NTP 2016)

				Scaled residuals[b]					
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	1.04	0.60	0.00	-0.49	0.83	37.76	7.77	4.18
Logistic	2	3.09	0.21	-0.28	1.41	1.41	40.25	16.36	10.83
LogLogistic[d,e]	***2***	***0.90***	***0.64***	***0.00***	***-0.46***	***0.75***	***37.62***	***8.47***	***2.95***
LogProbit[d]	3	0.99	0.80	0.00	-0.16	0.78	35.68	10.99	7.27
Multistage (1-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (2-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (3-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Probit	2	2.86	0.24	-0.22	1.38	1.38	39.91	15.35	10.31
Weibull[c]	2	1.04	0.59	0.00	-0.53	0.82	37.77	7.40	4.17

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Log Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-1. Fit of LogLogistic Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)

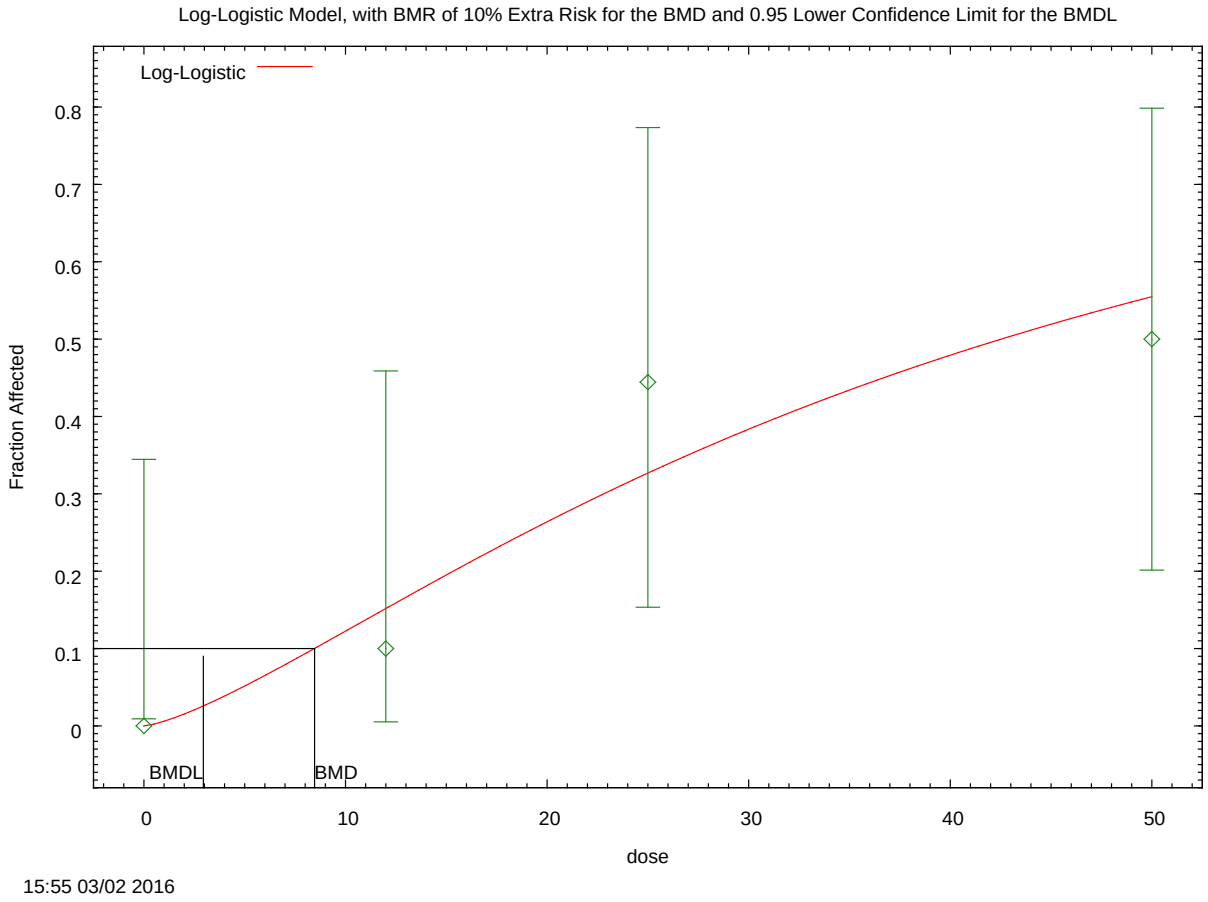


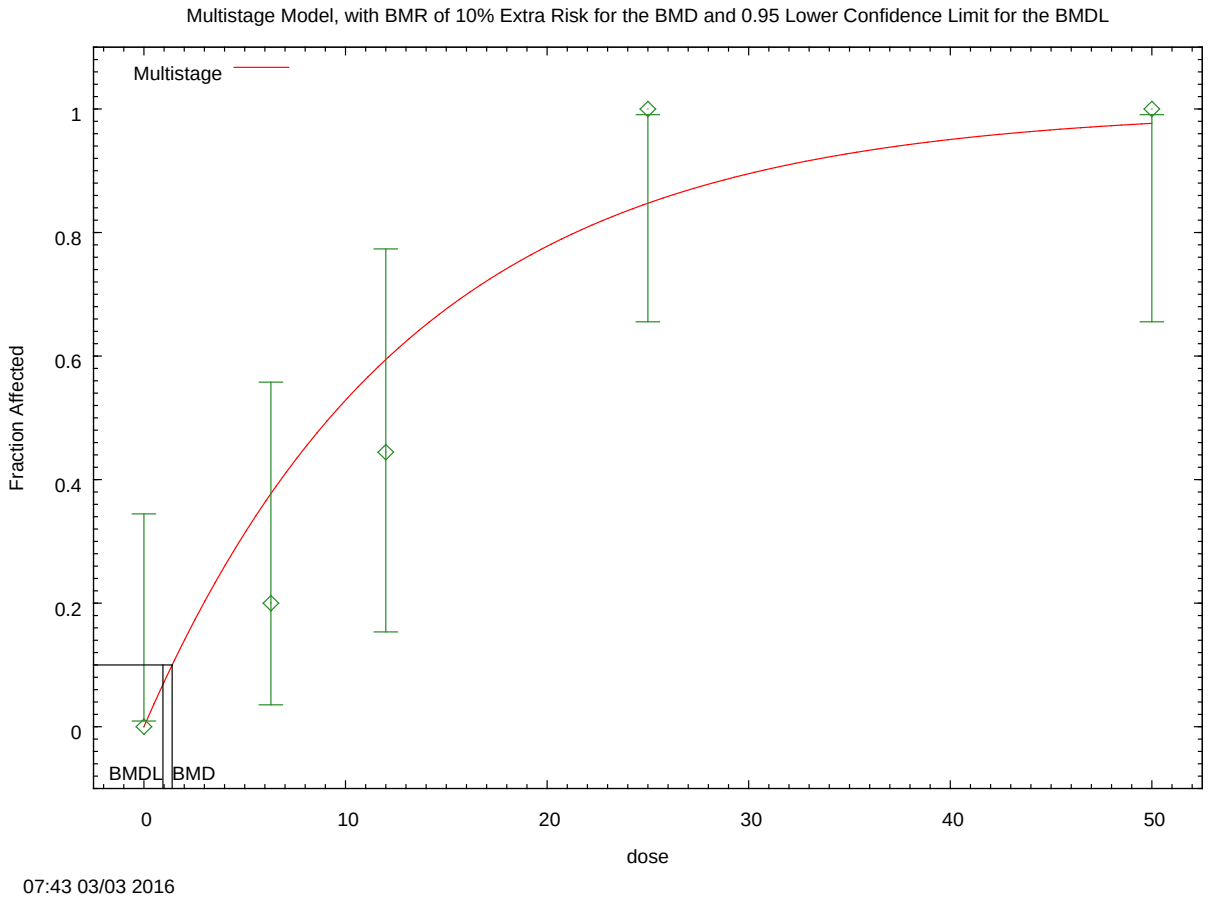
Table A-3. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Mice (Combined) Exposed to Antimony Trioxide (NTP 2016)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	3	1.04	0.79	0.00	0.48	-0.71	27.68	5.49	2.39
Logistic	3	0.85	0.84	-0.43	0.62	0.62	27.48	5.83	3.53
LogLogistic[d]	3	1.77	0.62	0.00	0.66	-0.86	28.64	5.79	3.17
LogProbit[d]	3	1.55	0.67	0.00	0.56	-0.89	28.31	5.73	3.25
Multistage (1-degree)[e,f]	***4***	***4.22***	***0.38***	***0.00***	***-1.16***	***-1.16***	***30.45***	***1.40***	***0.94***
Multistage (2-degree)[e]	4	0.70	0.95	0.00	0.05	0.59	25.41	4.41	1.74
Multistage (3-degree)[e]	3	0.27	0.97	0.00	0.24	-0.36	26.73	4.34	1.60
Multistage (4-degree)[e]	3	0.06	1.00	0.00	0.12	0.15	26.46	3.56	1.49
Probit	3	0.59	0.90	-0.34	0.51	0.51	27.12	5.48	3.28
Weibull[c]	3	0.61	0.89	0.00	0.48	-0.51	27.08	5.33	2.40

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Multistage 1 degree).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-2. Fit of 1-Degree Multistage Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Mice Exposed to Antimony Trioxide (mg Sb/m^3)



A summary of the potential PODs (BMCLs for the selected models, LOAELs, or NOAELs for models without adequate fit) is presented in Table A-4.

Table A-4. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Acute-Duration Inhalation MRL for Antimony

Endpoint (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Squamous metaplasia of the epiglottis in male and female rats (NTP 2016)	2.95 ($BMCL_{10}$)	0.162[c]	0.085
Chronic lung inflammation (NTP 2016)	12 (NOAEL)	0.545[c]	1.1
Squamous metaplasia of the epiglottis in male and female mice (NTP 2016)	0.94 ($BMCL_{10}$)	0.206[c]	0.035
Lung inflammation in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	0.203[d]	1.2
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	1.060[d]	6.2

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator with the average of the male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, and 4.0 kg for rabbits.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the NTP [2016] study and POD x 7 hours/24 hours x 5 days/7 days for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 1.4 µm (sigma g of 1.9).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9); this is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; RDDR = regional deposited dose ratio

Calculations

Intermittent Exposure: Concentrations tested in the NTP (2016) and Brieger et al. (1954) studies were adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days for NTP [2016] and 7 hours/day for Brieger et al. [1954]).

Human Equivalent Concentration: HECs were calculated for each potential POD by multiplying the POD_{ADJ} by the regional deposited dose ratio (RDDR) for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with the calculated average male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, for the NTP (2016) study and a reference body weight of 4.0 kg for the rabbits. The POD_{HEC} values are presented in Table A-4.

Uncertainty Factor:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = $BMCL_{HEC}$ ÷ uncertainty factors
0.001 mg Sb/m^3 = 0.0.035 mg Sb/m^3 ÷ 30

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There are limited data for comparing the relative toxicity of antimony compounds following acute inhalation exposure. The respiratory tract was a sensitive target in animals exposed to stibine, antimony trioxide, or antimony

trisulfide, but differences in the study designs do not allow for a direct comparison. Additionally, there are no data to allow for an assessment of the influence of valence state on the respiratory toxicity of antimony.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: The acute-duration inhalation MRL of 0.001 mg Sb/m^3 was adopted as the intermediate-duration inhalation MRL. The intermediate-duration database was not considered suitable for derivation of an MRL. An MRL based on the lowest POD_{HEC} estimated from an intermediate-duration study is slightly higher than the acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Information on the toxicity of inhaled antimony following intermediate-duration exposure primarily comes from a 13-week study in rats exposed to antimony trioxide (Newton et al. 1994) that identified the respiratory tract as the most sensitive effect and 6–10-week studies in rats, rabbits, and dogs (Brieger et al. 1954) that examined a limited number of endpoints and identified the respiratory tract and myocardium as the most sensitive endpoints. The systematic review identified the respiratory effects as presumed health effects in humans and myocardial damage and alterations in EKGs as suspected health effect in humans. In the Newton et al. (1994) study, exposure to ≥4.11 mg Sb/m^3 resulted in increases in alveolar/intra-alveolar macrophages, increases in relative lung weights, and increases in lung clearance half-times in rats killed at the end of the exposure period. In rats allowed to recover for 27 weeks, significant increases in the incidences of chronic interstitial inflammation and fibrosis were observed in rats exposed to 19.60 mg Sb/m^3. Mild congestion and focal hemorrhages were also observed in the lungs of rats exposed to 2.20 mg Sb/m^3 as antimony trisulfide for 6 weeks (Brieger et al. 1954); however, the investigators did not report the incidence of this effect, which precludes assessing the significance of the finding. Brieger et al. (1954) also found antimony trisulfide-induced alterations in EKGs and histological alterations in the myocardium of rats exposed to 2.20 mg Sb/m^3 for 6 weeks, dogs exposed to 3.98 mg Sb/m^3 for 10 weeks (no alterations were observed in dogs exposed to 3.81 mg Sb/m^3 for 7 weeks), and rabbits exposed to 4.02 mg Sb/m^3 for 6 weeks. A third intermediate-duration study reported unspecified lesions in the lungs, liver, kidneys, and pancreas (only qualitative data were provided), decreases in fertility, and decreases in litter size in rats exposed to 209 mg Sb/m^3 as antimony trioxide for 1.5–2 months (Belyaeva 1967).

The lung effects (increases in lung clearance time, chronic interstitial inflammation, and interstitial fibrosis) and the myocardial effects (histological alterations and altered EKGs) observed in the rats and rabbits were considered as the basis for an intermediate-duration MRL for antimony; the effects observed in dogs were not considered because reference values are not available for estimating the RDDR. BMD modeling was utilized to estimate the potential PODs for the histological alterations in the lungs observed in the Newton et al. (1994) study, but could not be utilized for the cardiac effects from the Brieger et al. (1954) studies due to the lack of incidence data. These incidence data were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option; see Appendix A for details on the BMD modeling results. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. For all lesion types, a BMR of 10% was used. The results of the BMD modeling for the chronic interstitial inflammation and lung fibrosis are presented in Tables A-5 and A-6 and the fits of the selected models are presented in Figures A-3 and A-4.

Table A-5. Model Predictions for the Incidence of Chronic Lung Interstitial Inflammation in Rats Exposed to Antimony Trioxide for 13 Weeks Followed by a 27-Week Recovery Period (Newton et al. 1994)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	1.01	0.60	0.66	-0.01	-0.75	277.38	2.97	0.69
Logistic	3	1.85	0.60	0.45	0.45	-0.93	276.71	0.87	0.61
LogLogistic[d]	2	1.02	0.60	0.66	0.00	-0.76	277.38	3.68	1.76
LogProbit[d]	2	1.02	0.60	0.66	0.00	-0.76	277.38	3.44	1.68
Multistage (1-degree)[f]	3	3.05	0.38	0.49	0.30	-1.30	278.32	0.64	0.43
Multistage (2-degree)[e]	2	0.79	0.67	0.56	-0.21	-0.59	277.19	1.81	0.59
Multistage (3-degree)[e]	2	0.53	0.77	0.43	-0.14	-0.52	276.90	1.33	0.57
Multistage (4-degree)[e]	2	0.47	0.79	0.39	-0.13	-0.50	276.83	1.19	0.55
Probit[f]	**3**	**1.23**	**0.75**	**0.46**	**-0.73**	**-0.73**	**275.81**	**0.95**	**0.66**
Weibull[c]	2	0.90	0.64	0.62	-0.08	-0.70	277.27	2.30	0.67

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Probit).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-3. Fit of Probit Model to Data on Incidence of Chronic Lung Interstitial Inflammation in Rats Exposed to Antimony Trioxide (mg Sb/m^3)

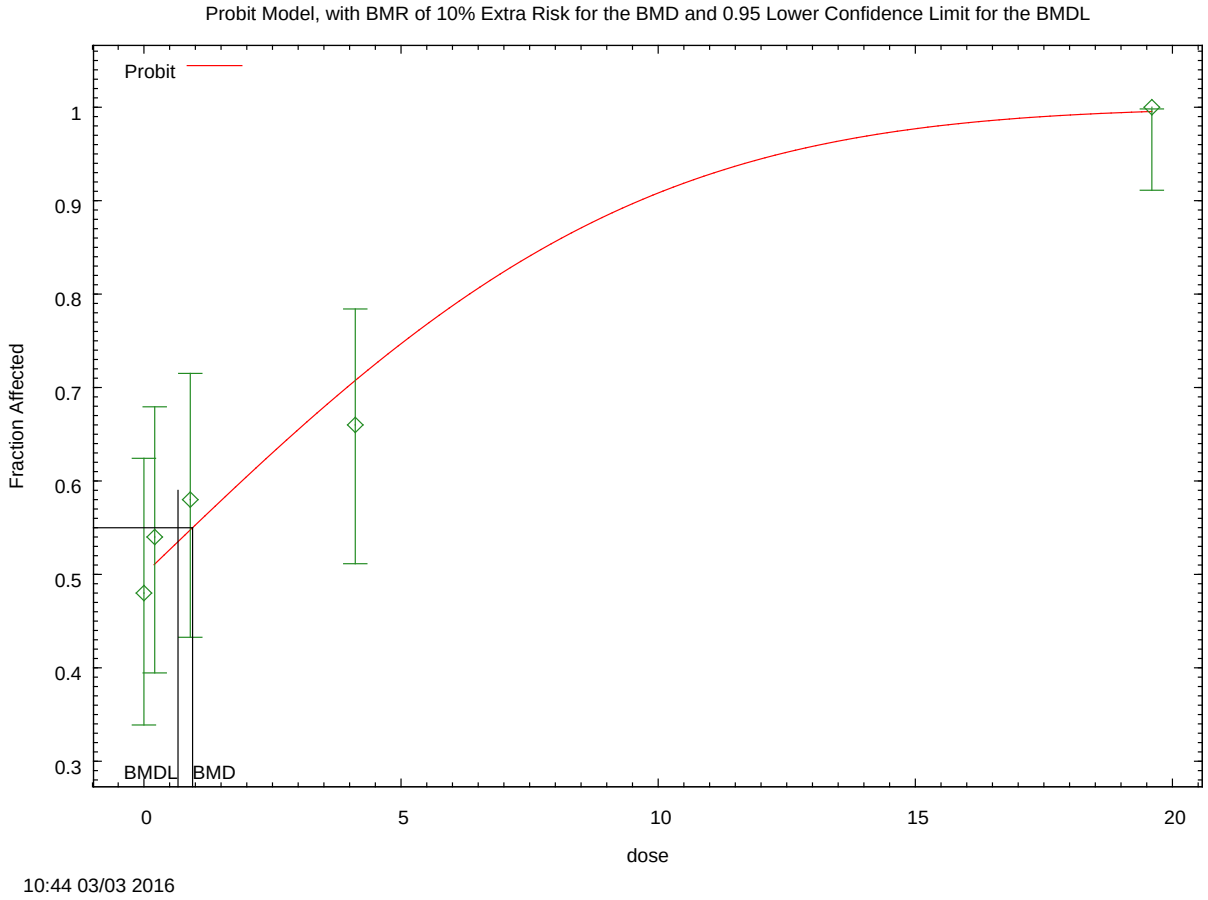


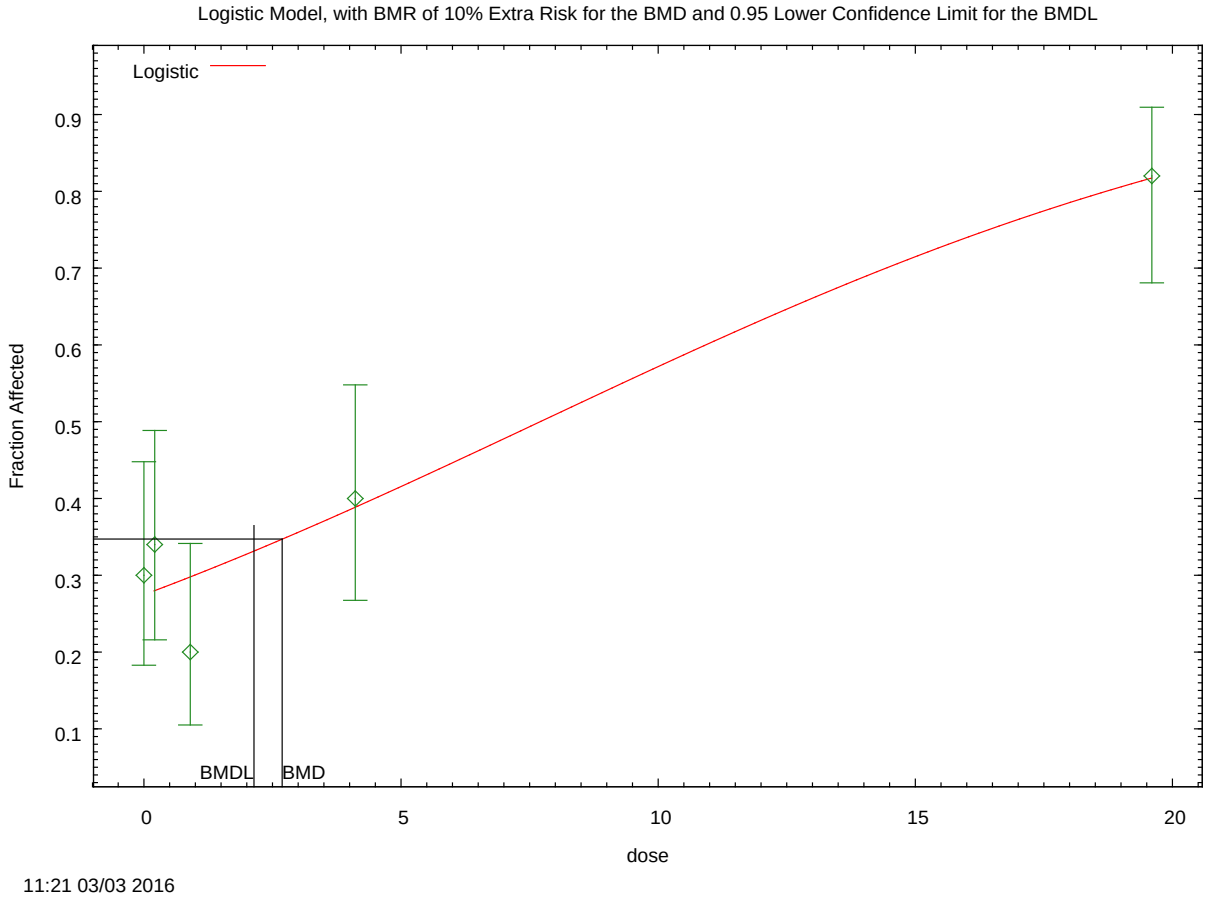
Table A-6. Model Predictions for the Incidence of Lung Fibrosis in Rats Exposed to Antimony Trioxide for 13 Weeks Followed by a 27-Week Recovery Period (Newton et al. 1994)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	2.97	0.23	-1.42	0.32	-1.42	298.77	3.40	1.31
Logistic[f]	***3***	***3.37***	***0.34***	***1.51***	***0.16***	***-1.51***	***297.19***	***2.69***	***2.14***
LogLogistic[d]	2	2.88	0.24	-1.38	0.22	-1.38	298.66	3.29	1.41
LogProbit[d]	2	2.69	0.26	-1.32	0.13	-1.32	298.45	3.25	2.08
Multistage (1-degree)[e]	3	4.56	0.21	-1.60	-0.52	-1.60	298.39	1.61	1.17
Multistage (2-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Multistage (3-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Multistage (4-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Probit	3	3.39	0.34	-1.52	0.16	-1.52	297.20	2.67	2.18
Weibull[c]	2	3.07	0.22	-1.45	0.33	-1.45	298.88	3.36	1.30

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-4. Fit of Logistic Model to Data on Incidence of Lung Fibrosis in Rats Exposed to Antimony Trioxide (mg Sb/m^3)



A summary of the PODs and HECs are presented in Table A-7. The POD_{HEC} values, which were based on $BMCL_{10}$ or NOAEL values, ranged from 0.19 to 0.078 mg Sb/m^3 and the POD_{HEC} values, based on LOAEL values, were 0.89 and 1.5 mg Sb/m^3. To compare the two types of PODs, the POD_{HEC} values based on LOAELs were divided by an uncertainty factor of 10 resulting in values of 0.15 and 0.089 mg Sb/m^3. The POD_{HEC} values for the increased lung clearance half-time, chronic lung interstitial inflammation, and degenerative heart effects and altered EKG readings in rabbits were similar, and the lowest value of 0.057 mg Sb/m^3 for chronic lung inflammation was selected as the basis of the MRL. This human equivalent value of 0.057 mg Sb/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.002 mg Sb/m^3. However, this MRL is slightly higher than the acute-duration inhalation MRL, and ATSDR adopted the acute-duration MRL of 0.001 mg Sb/m^3 for intermediate-duration exposure.

Table A-7. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Intermediate-Duration Inhalation MRL for Antimony

Endpoint (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Increased lung clearance half-times in rats (Newton et al. 1994)	0.902 (NOAEL)	0.487[c]	0.078
Chronic lung interstitial inflammation in rats (Newton et al. 1994)	0.66 ($BMCL_{10}$)	0.487[c]	0.057
Chronic lung fibrosis in rats (Newton et al. 1994)	2.14 ($BMCL_{10}$)	0.487[c]	0.19
Degenerative changes in heart and altered EKG readings in rats (Brieger et al. 1954)	2.20 (LOAEL)	3.185[d]	1.5
Degenerative changes in heart and altered EKG readings in dogs (Brieger et al. 1954)	3.98 (LOAEL)	NA[e]	NA
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	4.02 (LOAEL)	1.060[d]	0.89

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator, with estimated body weight of 0.230 kg for the Newton et al. (1994) study and reference body weights of 0.267 and 4.0 kg for rats and rabbits in the Brieger et al. (1954) study.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the Newton et al. [1994] study and 7 hours/day, 5 days/week for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 3.05 µm (sigma g of 1.57).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9), which is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.
[e]RDDR calculator does not have default values for dogs and HECs could not be calculated.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; RDDR = regional deposited dose ratio

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.0003 mg Sb/m^3
Critical Effect: Lung inflammation in rats
Reference: Newton et al. 1994
Point of Departure: $BMCL_{10}$ of 0.10 mg Sb/m^3
Uncertainty Factor: 30
LSE Graph Key: 16
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 0.0003 mg Sb/m^3 was derived for antimony based on an increased incidence of lung inflammation in female rats exposed to antimony trioxide 6 hours/day, 5 days/week for 12 months (Newton et al. 1994). The MRL is based on a $BMCL_{10}$ of 0.10 mg Sb.m^3 (human equivalent BMCL of 0.008 mg Sb/m^3) and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: The toxicity of airborne antimony has not been extensively studied in humans. Several occupational exposure studies have reported lung effects (pneumoconiosis, chronic bronchitis) in workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Signs of upper respiratory tract irritation including bleeding of the nose, rhinitis, upper airway inflammation, and laryngitis (Potkonjak and Pavlovich 1983; Renes 1953) have also been reported in workers. Other effects that have been observed in workers include altered EKGs (Brieger et al. 1954) and dermatitis, which is likely due to direct contact with skin (Potkonjak and Pavlovich 1983; Renes 1953). One study also reported reproductive disturbances and developmental effects (decreases in infant growth) in female workers exposed to metallic antimony, antimony trioxide, and antimony pentasulfide (Belyaeva 1967). Although some studies provided exposure levels, these studies were not considered suitable for derivation of a chronic MRL because many studies did not include control groups, wide ranges of antimony levels were reported, and many involved co-exposure to other compounds including arsenic.

A number of studies have evaluated the chronic toxicity of antimony compounds in rats and mice. These studies provide strong evidence that the respiratory tract is the primary target of antimony toxicity, which is supported by the systematic review of the toxicity data that concluded that respiratory tract toxicity is a presumed health effect in humans. The lowest LOAEL values were identified in three studies involving antimony trioxide exposure for 1–2 years (Newton et al. 1994; NTP 2016; Watt 1983). Higher LOAELs for lung effects were identified for other antimony compounds: 17.5 mg Sb/m^3 as antimony ore for interstitial fibrosis (Groth et al. 1986) and 84 mg Sb/m^3 as antimony trisulfide for lipoid pneumonia (Gross et al. 1952). Although these LOAELs are higher than those identified for antimony trioxide, the available data do not allow a comparison between compounds since adverse effects were often observed at the lowest concentration tested. A summary of the NOAEL and LOAEL values for the respiratory effects is presented in Table A-8. In addition to the pulmonary effects, effects have also been observed in the nasal cavity (respiratory epithelial hyperplasia), lymph nodes (lymphoid hyperplasia in bronchial and mediastinal lymph nodes), eyes (lenticular degeneration), and bone marrow (hyperplasia); the LOAELs for these effects (see Table A-8) are similar to those identified for respiratory effects.

Table A-8. Summary of NOAEL and LOAEL Values for Effects Observed in Target Tissues

NOAEL (mg Sb/m^3)	LOAEL (mg Sb/m^3)	Effect	Reference
Respiratory effects			
0.05	0.43	Chronic interstitial inflammation in female rats exposed to antimony trioxide for 1 year	Newton et al. 1994
	1.6	Focal fibrosis, pneumocyte hyperplasia in rats exposed to antimony trioxide for 55 weeks	Watt 1983
	2.5	Lung inflammation, proteinosis, alveolar epithelial hyperplasia, bronchiole epithelial hyperplasia, lung fibrosis in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Nasal respiratory epithelial hyperplasia in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Nasal respiratory epithelial inflammation in male mice exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Lung inflammation, alveolar fibrosis, pleural fibrosis and inflammation, alveolar and bronchiolar epithelial hyperplasia in mice exposed to antimony trioxide for 2 years	NTP 2016
0.43	3.8	Chronic interstitial inflammation in male rats exposed to antimony trioxide for 1 year	Newton et al. 1994
	17.5	Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony ore for 1 year	Groth et al. 1986
	36	Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony trioxide for 1 year	Groth et al. 1986
	84	Lipoid pneumonia in rats exposed to antimony trisulfide for 14.5 months	Gross et al. 1952
Bone marrow effects			
	2.5	Bone marrow hyperplasia in mice exposed to antimony trioxide for 2 years	NTP 2016
Lymphoreticular effects			
	2.5	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Lymphoid hyperplasia of bronchial lymph nodes in mice exposed to antimony trioxide for 2 years	NTP 2016
Ocular effects			
0.05	0.43	Lenticular degeneration in rats exposed to antimony trioxide for 1 year	Newton et al. 1994

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: Four studies identified LOAEL values of <5 mg Sb/m^3 for lung effects in rats (Newton et al. 1994; NTP 2016; Watt 1983) and mice (NTP 2016). Watt (1983) found increases in the incidence of focal fibrosis, adenomatous hyperplasia, cholesterol clefts, and pneumocyte hyperplasia in rats exposed to 1.6 mg Sb/m^3 for 55 weeks. In rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 2 years, inflammation, proteinosis, alveolar/bronchiolar hyperplasia, and fibrosis were observed in the lungs (NTP 2016). An increase in lung clearance times was observed in rats exposed to

3.8 mg Sb/m^3 as antimony trioxide for 12 months and an increase in the severity and incidence of chronic lung inflammation was observed at 0.43 (females only) and 3.8 mg Sb/m^3 was after a 1-year recovery period (Newton et al. 1994). Some non-respiratory effects have also been seen at similar concentrations, including lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 (Newton et al. 1994), bone marrow hyperplasia in mice exposed to 2.5 mg Sb/m^3 (NTP 2016), and lymphoid hyperplasia in bronchial and/or mediastinal lymph nodes in rats and mice exposed to 2.5 mg Sb/m^3 (NTP 2016). Newton et al. (1994) identified the lowest LOAEL value for chronic interstitial lung inflammation and lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 for 1 year with a 1-year recovery period; these effects were not observed at 0.05 mg Sb/m^3. The other chronic-duration studies identified higher LOAEL values.

Summary of the Principal Study:

Newton PE, Bolte HF, Daly IW, et al. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol 22(4):561-576.

Groups of 65 male and 65 female Fischer 344 rats were exposed to 0, 0.06, 0.51, or 4.50 mg/m^3 antimony trioxide dust (0, 0.05, 0.43, or 3.8 mg Sb/m^3, respectively) 6 hours/day, 5 days/week for 12 months followed by a 12-month observation period. Groups of five rats/sex were terminated after 6 and 12 months of exposure and at 6 months postexposure; the remaining animals were terminated 12 months postexposure. The MMAD was 3.76±0.84 µm with a geometric standard deviation of 1.79±0.326. The following parameters were used to assess toxicity: weekly detailed observations, body weight measurements (weekly for the first 13 weeks and monthly thereafter), ophthalmoscopic examination, hematological (hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, hemoglobin concentration, and volume, and total leukocyte counts) and clinical chemistry (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, fasting glucose, total protein, chloride, sodium, and potassium) indices assessed at 12, 18, and 24 months, and histopathological examination of the heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes.

No increases in mortality were observed. Corneal effects were observed during the study; however, the investigators noted that the effects were equally distributed among exposed and control groups and were similar to spontaneous degenerative conditions observed in Fischer 344 rats. The investigators noted a concentration-related increase in the occurrence of chromodacryorrhea (incidence data not provided); they noted that microscopic periodontal disease was also observed in some rats and that the chromodacryorrhea may be secondary to this effect. At the end of the recovery period, an increase in the occurrence of cataracts (focal posterior cataract, posterior subcapsular cataract, complete cataract) was observed (incidences of 6/55, 12/49, 18/64, and 19/60 were reported in Bio/Dynamics 1990); the incidence was statistically significant at ≥0.43 mg Sb/m^3 (Fisher Exact Test conducted by SRC). No treatment-related alterations in body weight gain, hematological indices, clinical chemistry indices, or lung weights were observed. At the end of the exposure period and at the end of the recovery period, statistically significant (Fisher Exact Test conducted by ATSDR) increases in the incidence of alveolar/intraalveolar macrophages were observed at ≥0.05 mg Sb/m^3. Histological alterations were observed in the lungs of rats killed at the end of the recovery periods: chronic interstitial inflammation at 0.43 (females only) and 3.8 mg Sb/m^3 and interstitial fibrosis at 3.8 mg Sb/m^3. Although a high incidence of lung inflammation was also observed in controls, the investigators noted that the inflammation observed in the controls was considered a “spontaneous lesion” and that the incidence and severity of the inflammation was concentration-related (see Table A-9). Increases in antimony trioxide lung clearance half-times were observed; the half-times (data reported in Bio/Dynamics 1990) in the male and female rats were 3.0 and 4.2 months, respectively, at 0.43 mg Sb/m^3 and 8.7 and 10.2 months, respectively, at 3.8 mg Sb/m^3, as compared to 2.5 and 2.2 months, respectively, in the 0.05 mg Sb/m^3 group. No significant increases in the incidence of neoplastic lesions were observed.

Table A-9. Incidence and Severity of Chronic Interstitial Lung Inflammation in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery

	Concentration (mg Sb/m^3)			
Severity	0	0.05	0.43	3.8
Males				
Minimal	4/52 (12.5)[a]	7/52 (18.9)	12/53 (33.3)	0/52 (0)
Slight	19/52 (59.4)	27/52 (73)	24/53 (66.7)	14/52 (29.2)
Moderate	8/52 (25)	3/52 (8.1)	0/53 (0)	32/52 (66.7)
Moderately severe	1/52 (3.1)	0/52 (0)	0/53 (0)	2/52 (3.8)
Females				
Minimal	3/49 (9.1)	12/52 (30)	14/54 (29.1)	1/50 (2.1)
Slight	24/49 (72.7)	23/52 (57.5)	23/54 (47.9)	29/50 (60.4)
Moderate	6/49 (18.2)	5/52 (12.5)	11/54 (22.9)	18/50 (37.5)
Moderately severe	0/49 (0)	0/52 (0)	0/54 (0)	0/50 (0)

[a]Percentage of total lesions with a specific severity score.

Source: Newton et al. 1994

Selection of the Point of Departure for the MRL: $BMCL_{10}$ of 0.10 mg Sb/m^3 ($BMCL_{HEC}$ of 0.008 mg Sb/m^3) for lung inflammation in female rats.

BMD modeling was utilized to estimate the potential PODs for the histological alterations observed in lungs and eyes. The incidence data from the Newton et al. (1994) (Table A-10) study were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. The results of the BMD modeling for lung inflammation in female rats is presented in Table A-11 and the model fit is presented in Figure A-5. The incidence data for lung inflammation in males were not considered suitable for modeling since only the highest concentration group showed a response; thus, the data provide limited information on the shape of the concentration-response curve. For lenticular degeneration, none of the available models provided an adequate fit to the data.

Table A-10. Incidence of Nonneoplastic Lesions in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery

	Concentration (mg Sb/m^3)			
Effect	0	0.05	0.43	3.8
Chronic lung inflammation in males	32/52	37/52	36/53	48/52[a]
Chronic lung inflammation in females	33/49	40/52	48/54[a]	48/50[a]
Lenticular degeneration	6/55	12/49	18/64[a]	19/60[a]

[a]Significantly different from controls.

Source: Newton et al. 1994

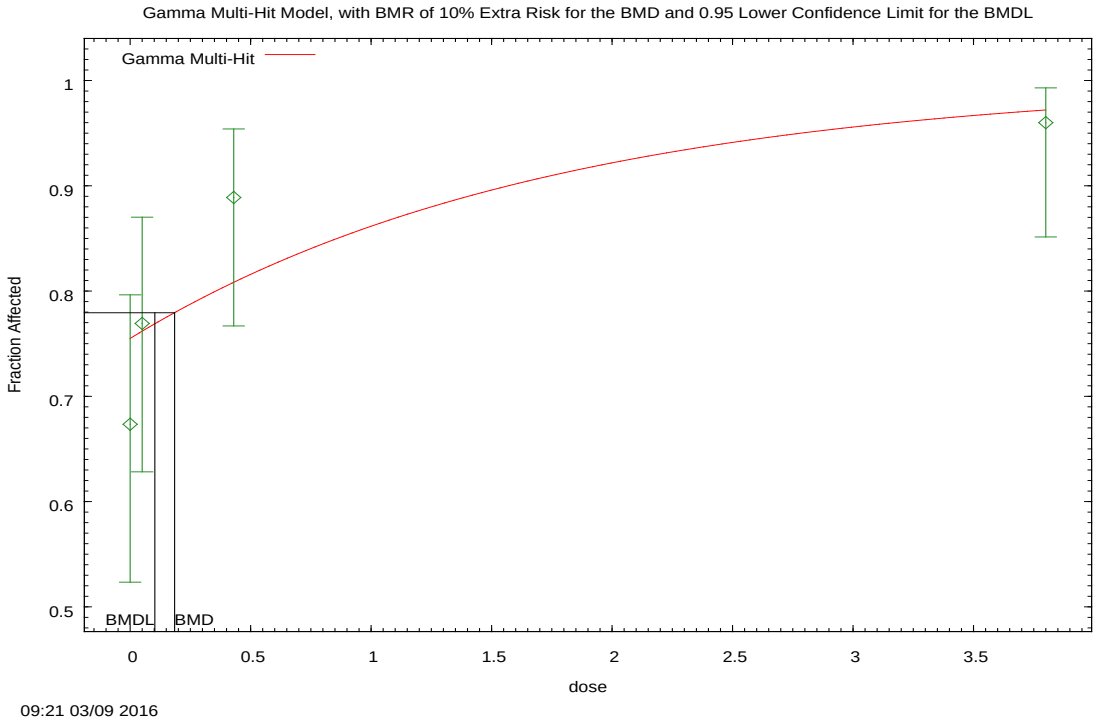
Table A-11. Model Predictions for Antimony Trioxide, Incidence of Chronic Lung Inflammation in Female Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery Period (Newton et al. 1994)

				Scaled residuals[b]					
Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c,d]	***2***	***4.3***	***0.12***	***0.13***	***1.51***	***1.51***	***181.03***	***0.18***	***0.10***
Logistic	2	4.63	0.10	0.07	1.56	1.56	181.38	0.22	0.13
LogLogistic[e,f]	2	1.15	0.56	-0.43	0.44	-0.81	177.59	0.04	0.01
LogProbit[d]	2	5.21	0.07	0.26	1.47	1.47	181.64	ND	ND
Multistage (1-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (2-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (3-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Probit	2	4.9	0.09	0.03	1.62	1.62	181.68	ND	ND
Weibull[c]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close; therefore the model with the lowest AIC was selected
[e]Slope restricted to ≥1.
[f]Model considered an outlier because the BMCL was 10 times lower than the other models.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-5. Fit of Gamma Model to Data on Incidence of Lung Interstitial Inflammation in Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)



The PODs for each endpoint are presented in Table A-12; for lung inflammation in males and lenticular degeneration, the NOAEL was used as the POD since the incidence data were not considered suitable for BMD modeling. The lowest POD_{HEC} was 0.008 mg Sb/m^3 for lung inflammation in female rats.

Table A-12. Summary of Potential Points of Departure (PODs) for Derivation of Chronic-Duration Inhalation MRL for Antimony

Endpoint (reference)	POD (mg Sb/m^3)	RDDR[a]	HEC[b] (mg Sb/m^3)
Chronic interstitial inflammation in male rats (Newton et al. 1994)	0.43 (NOAEL)	0.330	0.025
Chronic interstitial inflammation in female rats (Newton et al. 1994)	0.10 ($BMCL_{10}$)	0.436	0.008
Lenticular degeneration in rats (Newton et al. 1994)	0.05 (NOAEL)	2.797	0.025

[a]RDDR values specific for each region of the respiratory tract (pulmonary and extrarespiratory) were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats in the Newton et al. (1994) study and particle size of 3.76 µm (sigma g of 1.79).
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RDDR = regional deposited dose ratio

Calculations

Intermittent Exposure: Each potential POD was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days).

Human Equivalent Concentration: HECs were calculated by multiplying the POD_{ADJ} by the RDDR for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats and particle size of 3.76 μm (sigma g of 1.79). The POD_{HEC} values are presented in Table A-12.

Uncertainty Factor:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = POD_{HEC} ÷ uncertainty factors
0.0003 mg Sb/m^3 = 0.008 mg Sb/m^3 ÷ 30

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There are limited data to compare the relative toxicity of antimony compounds. Chronic studies have tested antimony trioxide, antimony trisulfide, and antimony ore; the respiratory tract was the most sensitive target in all of these studies. It is difficult to compare the potency of the different compounds because in most cases, the lowest concentration tested was a LOAEL. No data were available to compare the toxicity of trivalent and pentavalent antimony compounds.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Acute
MRL 1 mg Sb/kg/day
Critical Effect: Hepatocellular cytoplasmic vacuolization and forestomach focal ulceration
Reference: NTP 1992
Point of Departure: NOAEL of 99 mg Sb/kg/day
Uncertainty Factor: 100
LSE Graph Key: 2
Species: Mouse

MRL Summary: An acute-duration oral MRL of 1 mg Sb/kg/day was derived for antimony based on an increased incidence of cytoplasmic vacuolization in the liver and focal ulceration in the forestomach of mice exposed to antimony potassium tartrate in drinking water for 14 days (NTP 1992). The MRL is based on a NOAEL of 99 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Studies conducted in the 1920s and 1940s demonstrate that antimony potassium tartrate is a gastrointestinal irritant in humans (Dunn 1928) and animals (as reviewed by Elinder and Friberg 1986) resulting in vomiting and diarrhea shortly after exposure. Houpt et al. (1984) demonstrated that the mean latency to vomit was 30 minutes after dogs drank 4.8 mg Sb/kg as antimony potassium tartrate. These gastrointestinal effects are likely due to the antimony concentration rather than the dose. NTP (1992) evaluated the acute toxicity of antimony potassium tartrate in 14-day drinking water studies in rats and mice. In rats, the highest concentration (61 mg Sb/kg/day) did not result in significant alterations in body weight or histopathological alterations in major tissues and organs. In mice, exposure to 150 mg Sb/kg/day resulted in focal ulceration in the forestomach and minimal to moderate hepatocellular cytoplasmic vacuolization. Exposure to 99 and 150 mg Sb/kg/day resulted in a transient decrease in body weight gain; at termination, body weights were within 93% of controls. The decreases in body weight may have been secondary to the dramatic decrease in water intake, which was also observed in the exposed mice.

Selection of the Principal Study: Although the Houpt et al. (1984) study identified the lowest LOAEL for acute exposure, this study was not selected as the basis of the MRL because the study only evaluated overt signs of gastrointestinal irritation and was a single exposure study. The mouse NTP (1992) study was selected as the principal study for derivation of the MRL.

Summary of the Principal Study:

NTP. 1992. Toxicology studies of antimony potassium tartrate in F344/N rats and B6C3F1/N mice (drinking water and intraperitoneal injection studies). National Toxicology Program, Research Triangle Park, NC. NTP TOX 11.

This study is also reported in: Dieter MP, Jameson CW, Elwell MR. 1991. Comparative toxicity and tissue distribution of antimony potassium tartrate in rats and mice dosed by drinking water or intraperitoneal injection. J Toxicol Environ Health 34:51-82.

Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 0.30, 0.65, 1.25, 2.5, or 5.0 mg/mL antimony potassium tartrate (99–100% purity) in drinking water for 14 days. The investigators used water consumption data and body weight averages to calculate doses of 0, 59, 98, 174, 273, and 407 mg/kg/day antimony potassium tartrate (0, 21, 36, 63, 99, and 150 mg Sb/kg/day). The following parameters were evaluated to assess toxicity: twice daily observations, body weight measurements (days 1 and 8 and at termination), water consumption (days 7 or 8 and day 15), organ weights, histopathology of major tissues and organs in control and high-dose groups (five mice/sex/group) and all early deaths, and histopathological examination of the liver and forestomach of mice in all groups (five mice/sex/group).

One female mouse in the 150 mg Sb/kg/day group died prior to the end of the study. On day 8, decreases in body weight gain were observed in males exposed to 99 mg Sb/kg/day and in males and females exposed to 150 mg Sb/kg/day. However, by the end of the study, the final weights of all antimony groups were within 93% of the controls. Decreases in water consumption were observed at all antimony levels. The investigators noted that overt signs of toxicity (rough haircoat, emaciation, abnormal posture, hypoactivity, and decreased fecal material, consistent with avoidance of the antimony potassium tartrate containing water) were observed, but did not specify if this was observed in all groups. Histological alterations were observed in the forestomach and liver of mice in the 150 mg/kg/day group. In the forestomach, focal areas of ulceration with necrosis and inflammation of the squamous mucosa were observed; the incidence was not reported, although the investigators noted that gross forestomach lesions were observed in one male and three females. In the liver, minimal to moderate cytoplasmic vacuolization was observed in all mice in the 150 mg Sb/kg/day group; the vacuolization had a centrilobular distribution with some extension into portal areas.

Selection of the Point of Departure for the MRL: The NOAEL of 99 mg Sb/kg/day for liver lesions was selected as the POD for the MRL.

BMD modeling was not conducted since lesions were only observed in the high-dose group. The transient decrease in body weight observed at 99 and 150 mg Sb/kg/day was not selected as the POD because this decrease may have been the result of decreased water consumption likely due to taste aversion.

Uncertainty Factor:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL ÷ uncertainty factors
1 mg Sb/kg/day = 99 mg Sb/kg/day ÷ 100

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Support for identifying the liver as the critical effect for antimony is supported by intermediate-duration studies in which histological alterations were observed in rats exposed to antimony metal or antimony trioxide (Sunagawa 1981) and increases in alanine aminotransferase and aspartate aminotransferase in humans receiving injections of pentavalent antimony (Andersen et al. 2005). Insufficient evidence is available to allow for a comparison of the hepatotoxicity of different antimony compounds or valence states. The absorption rate of antimony potassium tartrate is greater than that of other antimony compounds (ICRP [1981] recommends rates of 10 and 1%, respectively), which likely results in a higher toxicity. More side effects (all effects) were observed in patients treated with antimony potassium tartrate than with pentavalent antimony compounds, although studies directly comparing the valency states on antimony hepatotoxicity were not identified. Alverez et al. (2005) reported greater cardiotoxicity and lethality in

guinea pigs receiving intramuscular injections of 10 mg Sb/kg/day as antimony potassium tartrate, as compared to guinea pigs administered 16 mg Sb/kg/day as meglumine antimoniate.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.0006 mg Sb/kg/day
Critical Effect: Decreased serum glucose in female rats
Reference: Poon et al. 1998
Point of Departure: NOAEL of 0.06 mg Sb/kg/day
Uncertainty Factor: 100
LSE Graph Key: 12
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.0006 mg Sb/kg/day was derived for antimony based on decreases in serum glucose levels in female rats exposed to antimony potassium tartrate in drinking water for 13 weeks (Poon et al. 1987). The MRL is based on a NOAEL of 0.06 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the intermediate-duration toxicity of antimony compounds. Observed effects include reductions in body weight gain, decreases in serum glucose levels, and developmental effects (decreased pup body weight and altered vasomotor response in pups). The NOAEL and LOAEL values for these effects are presented in Table A-13. The results of several 12–24-week studies provide evidence for compound-specific differences in toxicity that are likely reflective of differences in the relative absorption of the compounds. More soluble compounds such as antimony potassium tartrate and antimony trichloride appear to be more toxic than antimony trioxide.

Table A-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Exposure duration, compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)	Effect	Reference
Body weight effects				
GDs 1–22 Antimony trichloride (W)	0.07	0.7	Decreased maternal body weight gain (11%)	Marmo et al. 1987; Rossi et al. 1987
12 weeks Antimony metal (F)		85	Decreased body weight gain (10%)	Hiraoka 1986

Table A-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Exposure duration, compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)	Effect	Reference
13 weeks Antimony potassium tartrate (W)	42.17		No alterations in body weight gain	Poon et al. 1998
13 weeks Antimony trioxide (F)	1,408		No alterations in body weight gain	Hext et al. 1999
Serum glucose levels				
13 weeks Antimony potassium tartrate (W)	0.06	0.64	Decreases in serum glucose in female rats	Poon et al. 1998
Developmental effects				
LDs 0–22; PNDs 22–60 Antimony trichloride (W)		0.1 (post-weaning dose)	Altered vasomotor response in pups	Angrisani et al. 1988; Marmo et al. 1987
GDs 0–22; pups exposed on PNDs 22–60 Antimony trichloride (W)		0.1 (post-weaning dose)	Altered vasomotor response in pups	Rossi et al. 1987; Marmo et al. 1987
GDs 0–22; pups exposed on PNDs 22–60 Antimony trichloride (W)	0.07	0.7	Decreased pup growth on PNDs 10–60	Rossi et al. 1987

(F) = dietary exposure; GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (W) = drinking water exposure

Based on the limited available data, the toxicity of antimony potassium tartrate appears to be higher than antimony metal and antimony trioxide, which is likely due to the differences in absorption. ICRP (1981) recommends an absorption rate of 10% for antimony potassium tartrate and 1% for all other antimony compounds. A study (Alkhawajah et al. 1996) comparing the developmental toxicity of antimony trichloride (trivalent), sodium stibogluconate (pentavalent), and meglumine antimonate (pentavalent) in rats following intramuscular injections reported similar effects for the three compounds; although no direct comparisons were made, the magnitude of the alterations (decreases in fetal viability and body weight) appears to be similar for the three compounds.

Selection of the Principal Study: Three studies identified LOAEL values of 0.1–0.64 mg Sb/kg/day in rats exposed to antimony trichloride or antimony potassium tartrate. The effects observed at these concentrations included altered vasomotor response in rat pups exposed to antimony trichloride during

gestation and/or lactation and on PNDs 22–60 (Angrisani et al. 1988; Rossi et al. 1987), decreases in pup growth on PNDs 10–60 (Rossi et al. 1987), and decreases in serum glucose levels in rats exposed to antimony potassium tartrate for 13 weeks (Poon et al. 1998). These three endpoints were considered for the basis of the intermediate-duration MRL. Developmental toxicity and decreases in serum glucose levels were both considered suspected health effects in humans based on the systematic review of the available data on antimony; of the two developmental effects, only the decrease in growth was considered due to the uncertainty associated with estimating the dose for the vasopressor studies. In these studies, rats were exposed during gestation and/or lactation and then exposed on PNDs 22–60; the 0.1 mg Sb/kg/day dose is an estimate of the postnatal exposure, but does not include an estimate of prenatal exposure or exposure via breast milk.

Selection of the Point of Departure for the MRL: NOAEL of 0.06 mg Sb/kg/day for decreased serum glucose in female rats.

BMD modeling was considered for the decreases in serum glucose levels and decreases in pup body weight on PNDs 10 and 22. The serum glucose levels (Table A-14) and pup body weights (Table A-15) were fit to all available continuous models in EPA's BMDS (version 2.6.0). The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all models, a BMR of 1 standard deviation change from the control was used.

Table A-14. Serum Glucose Concentrations in Female Rats Exposed to Antimony Potassium Tartrate for 13 Weeks

Dose (mg Sb/kg/day)	Serum glucose concentration (mean±standard deviation, mg/dL)
0	242±55
0.06	217±22
0.64	200±25[a]
6.13	207±27[a]
45.69	198±25[a]

[a]Significantly different from controls.

Source: Poon et al. 1988

Table A-15. Alterations in Pup Body Weight on Postnatal Days (PNDs) 10 and 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation

	Pup body weight (mean±standard error)	
Dose (mg Sb/kg/day)	PND 10	PND 22
0	23±1.8 (73)[a]	58±5.1 (66)
0.07	20±2.6 (80)	52±4.0 (72)
0.7	17±0.4[b] (63)	31±2.8[b] (56)

[a]Number in parentheses is the number of pups examined; data were not presented in a way that would allow analysis on a per-litter basis.
[b]Significantly different from controls.

Source: Rossi et al. 1987

None of the models provided adequate fit to the serum glucose data or the PND 10 body weight data. Although adequate statistical fit was found for the PND 22 body weight data (model results are presented in Table A-16), the BMDL for the model with the lowest AIC (Exponential, model 3) was 0.72 mg Sb/kg/day, which is the same value as the empirical LOAEL identified in the study and was not considered a suitable basis for an MRL. Thus, a NOAEL/LOAEL approach was utilized to identify the POD for the intermediate-duration oral MRL. The NOAEL and LOAEL values for the decreased serum glucose level and the decreased pup body weight were similar and the endpoint with the lowest LOAEL (decreased serum glucose level) was selected as the basis of the MRL.

Table A-16. Model Predictions for Alterations in Pup Body Weight on Postnatal Day (PND) 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

				Scaled residuals[c]					
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
Constant variance									
Linear[e]	<0.0001	<0.0001	0.54	0.05	NA	-0.44	1,562.44	NA	NA
Nonconstant variance									
Exponential (model 2)[d]	<0.0001	0.61	0.27	0.03	NA	-0.31	1,540.28	1.32	0.86
Exponential (model 3)[d,e]	***<0.0001***	***0.61***	***0.27***	***0.03***	***NA***	***-0.31***	***1,540.28***	***1.32***	***0.72***
Exponential (model 4)[d]									ND
Exponential (model 5)[d]									ND
Hill[d]									ND
Linear[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.81

Table A-16. Model Predictions for Alterations in Pup Body Weight on Postnatal Day (PND) 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Polynomial (2-degree)[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.80
Power[d]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.71

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model did not provide adequate fit to the variance data. With nonconstant variance model applied, all models (except for the Exponential 4, and 5, and Hill models) provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Exponential 3; the Exponential 2 and 3 had the same AIC, so the model with the more conservative BMDL was selected out of these two).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined (BMDL computation failed); SD = standard deviation

Summary of the Principal Study:

Poon R, Chu I, Lecavalier P, et al. 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food Chem Toxicol 36:21-35.

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0, 0.5, 5, 50, or 500 ppm antimony as potassium antimony tartrate (99.95% pure) in drinking water for 13 weeks. Based on average water consumption and body weight data, the investigators calculated antimony doses of 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day in males and 0, 0.06, 0.64, 6.13, and 45.69 mg Sb/kg/day in females. An additional group of 10 male and 10 female rats was exposed to 0 or 500 ppm for 13 weeks followed by a 4-week recovery period. The following parameters were used to assess toxicity: weekly body weight, food consumption, and water intake measurements; hematological indices (erythrocyte counts hemoglobin, hematocrit, mean corpuscular volume, and total and differential leukocyte counts); clinical chemistry indices (albumin, alkaline phosphatase, aspartate aminotransferase, creatine kinase, sorbitol dehydrogenase, bilirubin, calcium, cholesterol, creatinine, glucose, inorganic phosphate, lactic dehydrogenase, total protein, urea nitrogen, and uric acid); serum thyroxin and thyroid hormone binding ratio; organ weights (brain, thymus, heart, kidney, spleen, liver); and histopathological examination (brain, pituitary, thyroid and trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, esophagus, stomach, small and large intestine, urinary bladder, skin, bone marrow, and gonadal tissues).

No alterations in survival or overt signs of toxicity were observed. Decreases in water consumption (35% lower than controls) and food consumption (12%) were observed in the 42.17/45.69 mg Sb/kg/day group during the exposure period but not during the recovery period.

- Body weight: A decrease in body weight gain, significant in males starting at week 6 and females at week 12, was observed at 42.17/45.69 mg Sb/kg/day; the body weights appeared to be within 10% of the controls. A significant increase in relative kidney weights was observed in the 42.17/45.69 mg Sb/kg/day group.
- Metabolic: A dose-related decrease (15–17%) in serum glucose levels was observed in females exposed to ≥0.64 mg Sb/kg/day; lower values were also observed in the males, but were not statistically different from controls. No differences in serum glucose levels were observed at the end of the recovery period. ATSDR notes that serum glucose levels in all groups (including controls) were higher than the range of normal values reported by the animal supplier (Charles River Laboratories 2006).
- Clinical chemistry: Decreases in serum creatinine levels and alkaline phosphatase levels were observed in males and females exposed to 42.17/45.69 mg Sb/kg/day at the end of the exposure period, but not at the end of the observation period. A decrease (24%) in serum cholesterol level was observed in females exposed to 45.69 mg Sb/kg/day; the toxicological significance of this alteration is not known.
- Hematological: Decreases in red blood cells and platelet counts and increases in mean corpuscular volume were observed in males exposed to 42.17 mg Sb/kg/day; in females, the only hematological alteration was an increase in monocytes at 45.69 mg Sb/kg/day. Significant increases in hepatic ethoxyresorufin-O-deethylase and glutathione-S-transferase activities were observed in males at 42.17 mg Sb/kg/day; glutathione-S-transferase activity was also increased in females at 45.69 mg Sb/kg/day.
- Hepatic: Histological alterations included anisokaryosis in the liver in all antimony exposed groups; dose-related increases in the severity were also observed. Anisokaryosis was also observed at the end of the recovery period. Other hepatic effects included an increase in hepatocellular portal density in all antimony groups and minimal nuclear hyperchromicity at ≥0.56/0.64 mg Sb/kg/day, but there was not consistent dose-response relationship for this endpoint. The severity scores for the anisokaryosis were 0.1, 0.6, 1.0, 1.9, and 2.8 in the 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day males; a severity score of 1 is considered minimal, 2 is mild, and 3 is moderate. In the females, the respective severity scores were 0.9, 1.5, 2.3, 2.3, and 2.6. Similarly, the increase in portal density in the hepatocellular cytoplasm was graded as minimal at the two lowest doses in the males and females and mild at the two highest doses. The anisokaryosis, hepatocellular density, and hyperchromicity are considered adaptive changes and were not considered adverse.
- Skeletal: In the bone marrow, an increase in myeloid hyperplasia was observed at ≥5.58 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females.
- Spleen: The following alterations were observed in the spleen: sinus congestion at ≥0.56 mg Sb/kg/day in males, sinus hyperplasia at 42.17 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females, and arterial cuff atrophy at 42.17 mg Sb/kg/day in males. In the recovery period, increases in incidence of sinus congestion (males only), arterial cuff atrophy, periarteriolar lymphocyte sheath cell density, and sinus hematopoiesis were observed.
- Endocrine: Statistically significant increases in thyroid hormone binding ratio were observed in females at 6.13 and 45.69 mg Sb/kg/day. Thyroid histological alterations included an increase in epithelial height, reduced follicle size, and nuclear vesiculation in antimony rats; an increased occurrence of collapsed follicles was observed in the antimony recovery group. These thyroid effects did not show a strong dose-response relationship and did not appear to affect thyroid function; the investigators did not consider them adverse.

Uncertainty Factor:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL ÷ uncertainty factors
0.006 mg Sb/kg/day = 0.06 mg Sb/kg/day ÷ 100

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The MRL is based on health effects observed in animals exposed to soluble antimony compounds; it is likely that oral exposure to insoluble antimony compounds would result in adverse effects occurring at higher dose levels.

Agency Contacts (Chemical Managers): Melanie Buser

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The chronic-duration oral database was considered inadequate for derivation of an MRL. The two available studies examined a limited number of endpoints and decreases in survival were observed in the only doses tested.

Rationale for Not Deriving an MRL: Two studies have evaluated the chronic toxicity of antimony (Kanisawa and Schroeder 1969; Schroeder et al. 1970) in rats and mice exposed to antimony potassium tartrate in drinking water for a lifetime. Decreases in survival were observed in rats exposed to 0.63 mg Sb/kg/day (Schroeder et al. 1970) and in mice exposed to 0.35 mg Sb/kg/day (Kanisawa and Schroeder 1969). Both studies examined a limited number of endpoints. In rats, no cardiovascular or body weight alterations were observed; however, a decrease in nonfasting glucose levels was found at 0.63 mg Sb/kg/day. No hepatic or body weight alterations were observed in mice. Given the limited number of endpoints examined and decreases in survival at the only dose tested, neither study was considered suitable for derivation of a chronic-duration oral MRL.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ANTIMONY

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for antimony. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of antimony have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of antimony are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for antimony released for public comment in 2017. The following main databases were searched in January 2018:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for antimony. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases

were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to antimony were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
01/2018	((7440-36-0[rn] OR 1315-04-4[rn] OR 1314-60-9[rn] OR 28300-74-5[rn] OR 10025-91-9[rn] OR 1309-64-4[rn] OR 1345-04-6[rn] OR 7803-52-3[rn]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[mhda])) OR (("Antimony"[tw] OR "Antimonyl potassium tartrate"[tw] OR "Potassium antimonyl tartrate"[tw] OR "Sb2O3"[tw] OR "Senarmontite"[tw] OR "Potassium antimonyltartrate"[tw] OR "Stibine"[tw] OR "Stibium"[tw] OR "Stibnite"[tw] OR "Tartar emetic"[tw] OR "Trichlorostibine"[tw] OR "Valentinite"[tw]) NOT medline[sb]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[crdat] OR 2015/02/01:3000[edat]))
	("A 1550"[tw] OR "A 1582"[tw] OR "A 1588LP"[tw] OR "A 2550"[tw] OR "AGO 40"[tw] OR "Amspec-KR"[tw] OR "AN 800"[tw] OR "Anchimonzol A 2550"[tw] OR "Antimonate(2)-, bis(mu-tartrato(4-))di-, dipotassium, trihydrate"[tw] OR "Antimonate(2-), bis(mu-(2,3-di(hydroxy-kappaO)butanedioato(4-)-kappaO1:kappaO4))di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis(mu-(2,3-dihydroxybutanedioato(4-)-O(sup 1),O(sup 2):O(sup 3),O(sup 4)))-di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis(u-(2,3-dihydroxybutanedioato(4-)-O1,O2,O3,O4))di-, dipotassium, trihydrate"[tw] OR "Antimonate(2-), bis[.mu.-[2,3-di(hydroxy-,kappa.O)butanedioato(4-)-.kappa.O(1):.kappa.O4]]di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis[.mu.-[2,3-di(hydroxy-.kappa.O)butanedioato(4-)-.kappa.O1:.kappa.O4]]di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonial saffron"[tw] OR "Antimonic oxide"[tw] OR "Antimonic sulfide"[tw] OR "Antimonious oxide"[tw] OR "Antimonous chloride"[tw] OR "Antimonous sulfide"[tw] OR "Apox S"[tw] OR "AT 3 (fireproofing agent)"[tw] OR "AT 3B"[tw] OR "Atox B"[tw] OR "Atox F"[tw] OR "Atox R"[tw] OR "Atox S"[tw] OR "C.I. 77060"[tw] OR "C.I. Pigment Red 107"[tw] OR "C.I. Pigment White 11"[tw] OR "Chemetron fire shield"[tw] OR "CI 77060"[tw] OR "CI Pigment Red 107"[tw] OR "CI Pigment white 11"[tw] OR "Dechlorane A-O"[tw] OR "Diantimony pentaoxide"[tw] OR "Diantimony pentasulphide"[tw] OR "Diantimony pentoxide"[tw] OR "Diantimony trioxide"[tw] OR "Diantimony trisulfide"[tw] OR "Dipotassium bis(mu-(L-(+)-tartrato(4-)))diantimonate(2-) trihydrate"[tw] OR "ENT 50,434"[tw] OR "Exitelite"[tw] OR "Fireshield FSPO 405"[tw] OR "FireShield H"[tw] OR "FireShield LS-FR"[tw] OR "Flame Cut 610"[tw] OR "Flame Cut 610R"[tw] OR "Flameguard VF 59"[tw] OR "HFR 201"[tw] OR "HM 203P"[tw] OR "Hydrogen antimonide"[tw] OR "LS-FR"[tw] OR "LSB 80"[tw] OR "Microfine A 05"[tw] OR "NCI-C55152"[tw] OR "Nyacol 1550"[tw] OR "Nyacol A 1510LP"[tw] OR "Nyacol A 1530"[tw] OR "Nyacol A 1590"[tw] OR "Nyacol ADP 480"[tw] OR "Nyacol ADP 494"[tw] OR "Nyacol AGO 40"[tw] OR "Octoguard FR 10"[tw] OR "Patox C"[tw] OR "Patox H"[tw] OR "Patox L"[tw] OR "Patox M"[tw] OR "Patox S"[tw] OR "Potassium antimonyl D-tartrate"[tw] OR "Sanka Anchimonzol A 2550M"[tw] OR "Stibic anhydride"[tw] OR "Stibiox MS"[tw] OR "Sun Epoch NA 100"[tw] OR "Sun Epoch NA 3070P"[tw] OR "Sun Epoch NA 3080P"[tw] OR "Suncolloid AME 130"[tw] OR "Suncolloid AMT 130"[tw] OR "Thermoguard B"[tw] OR "Thermoguard L"[tw] OR "Thermoguard S"[tw] OR "Timonox"[tw] OR "Timonox White

Table B-2. Database Query Strings

Database search date	Query string
	Star"[tw] OR "Twinkling star"[tw]) NOT medline[sb]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[crdat] OR 2015/02/01:3000[edat])
Toxline	
01/2018	((7440-36-0 [rn] OR 1315-04-4 [rn] OR 1314-60-9 [rn] OR 28300-74-5 [rn] OR 10025-91-9 [rn] OR 1309-64-4 [rn] OR 1345-04-6 [rn] OR 7803-52-3 [rn]) OR "antimony" OR "antimonyl potassium tartrate" OR "potassium antimonyl tartrate" OR "sb2o3" OR "senarmontite" OR "potassium antimonyltartrate" OR "stibine" OR "stibium" OR "stibnite" OR "tartar emetic" OR "trichlorostibine" OR "valentinite") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("anchimonzol a 2550" OR "antimonial saffron" OR "antimonic oxide" OR "antimonic sulfide" OR "antimonious oxide" OR "antimonous chloride" OR "antimonous sulfide" OR "apox s" OR "atox b" OR "atox f" OR "atox r" OR "atox s" OR "chemetron fire shield" OR "dechlorane a o" OR "diantimony pentaoxide" OR "diantimony pentasulphide" OR "diantimony pentoxide" OR "diantimony trioxide" OR "diantimony trisulfide" OR "ent 50 434" OR "exitelite" OR "fireshield fspo 405" OR "fireshield h" OR "fireshield ls fr" OR "flame cut 610" OR "flame cut 610r" OR "flameguard vf 59" OR "hfr 201" OR "hm 203p" OR "hydrogen antimonide" OR "ls fr" OR "lsb 80" OR "microfine a 05" OR "nci c55152" OR "nyacol 1550" OR "nyacol a 1510lp" OR "nyacol a 1530" OR "nyacol a 1590" OR "nyacol adp 480" OR "nyacol adp 494" OR "nyacol ago 40" OR "octoguard fr 10" OR "patox c" OR "patox h" OR "patox l" OR "patox m" OR "patox s" OR "potassium antimonyl d tartrate" OR "sanka anchimonzol a 2550m" OR "stibic anhydride" OR "stibiox ms" OR "sun epoch na 100" OR "sun epoch na 3070p" OR "sun epoch na 3080p" OR "suncolloid ame 130" OR "suncolloid amt 130" OR "thermoguard b" OR "thermoguard l" OR "thermoguard s" OR "timonox" OR "timonox white star" OR "twinkling star") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
01/2018	FILE 'TOXCENTER' ENTERED AT 08:52:47 ON 10 JAN 2018 => s 7440-36-0 OR 1315-04-4 OR 1314-60-9 OR 28300-74-5 OR 10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 7803-52-3 L1 22076 7440-36-0 OR 1315-04-4 OR 1314-60-9 OR 28300-74-5 OR 10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 7803-52-3 => s l1 not tscats/fs L2 21927 L1 NOT TSCATS/FS => s l2 not patent/dt L3 17767 L2 NOT PATENT/DT => s l3 and py>2014 L4 1973 L3 AND PY>2014 => s l3 and 20141201 L5 0 L3 AND 20141201 => s l3 and ed>=20141201 L6 2222 L3 AND ED>=20141201 => activate toxquery/q

Table B-2. Database Query Strings

Database search date	Query string
	L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT)
	L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? ORSPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (NONHUMAN MAMMALS)/ORGN L37 QUE L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 => s l6 and l39 L40 1007 L6 AND L39 => s l40 and medline/fs L41 141 L40 AND MEDLINE/FS => s l40 and biosis/fs L42 185 L40 AND BIOSIS/FS => s l40 and caplus/fs L43 681 L40 AND CAPLUS/FS => s l40 not (medline/fs or biosis/fs or caplus/fs) L44 0 L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) => dup rem l41 l42 l43 => s l45 not medline/fs L46 141 S L45 L47 169 S L45 L48 597 S L45 3757645 MEDLINE/FS L49 766 (L46 OR L47 OR L48) NOT MEDLINE/FS => d scan l49

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
01/2018	Compounds searched: 7440-36-0; 1315-04-4; 1314-60-9; 28300-74-5; 10025-91-9; 1309-64-4; 1345-04-6; 7803-52-3
NTP	
05/2019	"antimony" "stibine" "7440-36-0" "1309-64-4" "1315-04-4" "1314-60-9" "28300-74-5" "10025-91-9" "1345-04-6" "7803-52-3" "antimonyl potassium tartrate" "potassium antimonyl tartrate" "sb2o3" "senarmontite" "potassium antimonyltartrate" "stibium" "stibnite" "tartar emetic" "trichlorostibine" "valentinite"
NIH RePORTER	
05/2019	Text Search: "Antimony" OR "Antimonyl potassium tartrate" OR "Potassium antimonyl tartrate" OR "Sb2O3" OR "Senarmontite" OR "Potassium antimonyltartrate" OR "Stibine" OR "Stibium" OR "Stibnite" OR "Tartar emetic" OR "Trichlorostibine" OR "Valentinite" OR "Antimonial saffron" OR "Antimonic oxide" OR "Antimonic sulfide" OR "Antimonious oxide" OR "Antimonous chloride" OR "Antimonous sulfide" OR "Diantimony pentaoxide" OR "Diantimony pentasulphide" OR "Diantimony pentoxide" OR "Diantimony trioxide" OR "Diantimony trisulfide" OR "Hydrogen antimonide" OR "Potassium antimonyl D-tartrate" OR "Stibic anhydride" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,465
- Number of records identified from other strategies: 40
- Total number of records to undergo literature screening: 1,505

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on antimony:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

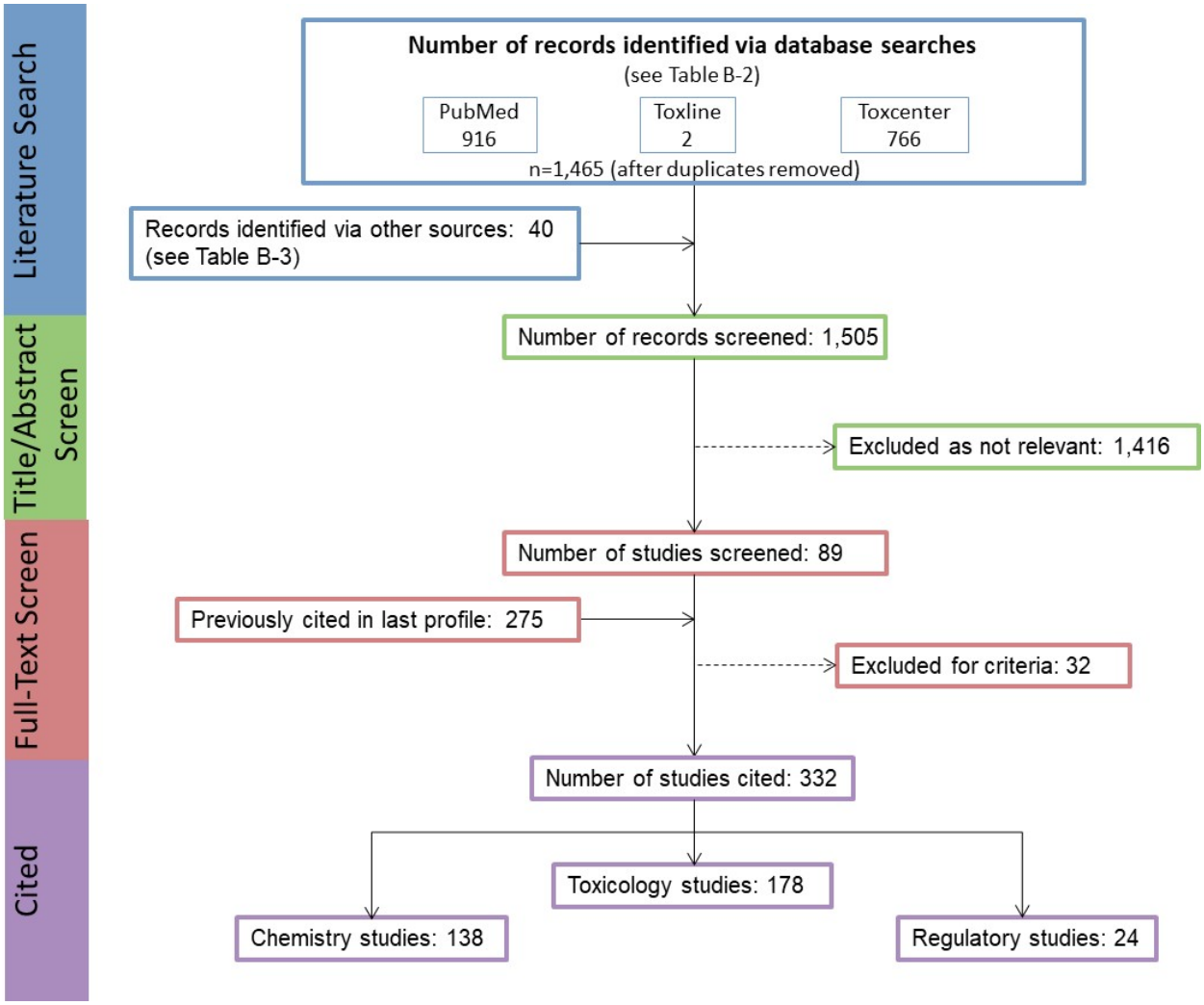
- Number of titles and abstracts screened: 1,505
- Number of studies considered relevant and moved to the next step: 89

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 89
- Number of studies cited in the pre-public draft of the toxicological profile: 275
- Total number of studies cited in the profile: 332

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2018 Literature Search Results and Screen for Antimony



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ANTIMONY

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to antimony, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to antimony:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony. The inclusion criteria used to identify relevant studies examining the health effects of antimony are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of antimony. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for antimony released for public comment in 2017. See Appendix B for the databases searched and the search strategy.

A total of 1,505 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of antimony.

Title and Abstract Screen. In the Title and Abstract Screen step, 1,505 records were reviewed; 14 studies were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 14 health effects studies identified in the update literature was performed. Additionally, 71 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 85.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Antimony and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-3, 2-4, and 2-5, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for antimony identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited number of endpoints and reported respiratory, cardiovascular, gastrointestinal, musculoskeletal, immunological, reproductive, and developmental effects. Animal studies examined a number of endpoints following inhalation, oral, or dermal exposure. These studies examined most systemic endpoints and reported respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, and metabolic effects. Additionally, animal studies have reported immunological, reproductive, and developmental effects.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Antimony Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Observational		7	2 (1)	3					3	1		1	2	1	1		2
		5	2	3					3	1		1	1	1	1		1
Experimental																	
Oral studies																	
Observational	1	1	5(0)	1		1	1				1	1	5	1	2[a]	2	3
	0	0	3	1		1	0				0	1	1	0	0	1	1
Experimental																	
Dermal studies																	
Observational																	
Experimental																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

Numbers in parentheses represent those studies looking at the specific cardiovascular endpoints of interest to this systematic review (damage to the myocardium and/or EKG alterations).

[a]One study (Zheng et al. 2014) was excluded because it measured risk of "adverse pregnancy outcome," but did not provide information on the endpoints examined and was not considered suitable for the systematic review.

1

APPENDIX C

Table C-4. Overview of the Health Outcomes for Antimony Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	3	5	2(1)				2	3			2						
	0	5	1				1	2			0						
Intermediate-duration	5	4	5		5		3	2			1			1	1		
	0	4	3		1		2	1			1			1	1		
Chronic-duration	7	8	7	6	1	4	6	6		2	6	6	5	6		4	7
	2	7	2	1	0	2	0	1		2	0	3	0	0		0	5
Oral Studies																	
Acute-duration	3	2	2	3		2	2	2			2						
	1	1	0	2		0	1	0			0						
Intermediate-duration	11	2	4(2)	3	7	1	4	3	1	1	2	1		4	3	1	
	5	0	1	0	4	0	2	0	0	0	0	1		0	3	1	
Chronic-duration	2		1(0)				1									1	2
	0		0				0									1	0
Dermal studies																	
Acute-duration									1	4		1					
									0	2		0					
Intermediate-duration	1		1				1	1	1	1				1			
	0		0				0	0	0	1				0			
Chronic-duration									4	3							
									1	0							

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

Numbers in parentheses represent those studies looking at the specific cardiovascular endpoints of interest to this systematic review (damage to the myocardium and/or EKG alterations).

Respiratory, cardiovascular (damage to the myocardium and/or EKG alterations), gastrointestinal, metabolic (alterations in blood glucose levels), and developmental effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Eighty-five studies (published in 54 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of antimony health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to antimony and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

Table C-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects							
Cohort studies							
Jones 1994 (antimony metal and antimony trioxide)	–	–	+	NA	–	+	Second
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Schnorr et al. 1995 (antimony oxides)	+	–	+	–	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second
Cooper et al. 1968 (antimony trioxide)	NA	–	+	NA	+	+	Second
Case series							
Potkonjak and Pavlovich 1983 (antimony oxides)	NA	–	+	NA	+	+	Second
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Cardiovascular effects (myocardium damage and/or EKG alterations)							
Cross Sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	-	+	+	+	+	Second
Outcome: Gastrointestinal Effects							
Cohort studies							
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second

APPENDIX C

Table C-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Case series							
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Developmental Effects							
Cohort studies							
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	–	–	+	+	–	+	Second
Case-control studies							
Longerich et al. 1991 (not reported)	+	–	+	–	+	+	Second
Cross-sectional studies							
Bloom et al. 2015	NA	-	+	-	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects (inhalation only)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit) (antimony trisulfide)	NA	NA	NA	NA	+	-	**+**	+	NA	Second
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NIOSH 1979 (rat, stibine)	–	+	+	+	+	+	**–**	–	NA	Second
NIOSH 1979 (guinea pig, stibine)	–	+	+	+	+	+	**–**	–	NA	Second
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	**–**	+	NA	Second
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	**+**	+	NA	Second
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	**–**	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	**+**	+	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
Gross et al. 1952 (rat, antimony trisulfide)	–	+	+	–	+	–	+	+	NA	First
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Outcome: Cardiovascular effects(myocardium damage and/or EKG alterations)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Inhalation intermediate exposure										
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second

APPENDIX C

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	–	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pigs, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Oral acute exposure										
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	+	NA	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	++	+	+	++	**+**	+	NA	First
Outcome: Gastrointestinal effects										
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	**+**	–	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	**+**	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	**+**	++	NA	First
Oral acute exposure										
Houpt et al. 1984 (dog, antimony potassium tartrate)	–	+	+	+	+	–	**+**	+	NA	First
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	+	+	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	**+**	–	NA	First
Outcome: Metabolic effects (altered blood glucose levels)										
Oral intermediate exposure										
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	**+**	–	NA	First
Oral chronic exposure										
Schroeder et al. 1970 (rat, antimony potassium tartrate)	+	+	+	+	+	–	**+**	–	NA	First
Outcome: Developmental effects										
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	**–**	+	NA	Second
Oral intermediate exposure										
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First

APPENDIX C

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Rossi et al. 1987 (rat, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First
Rossi et al. 1987 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to antimony and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Antimony—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Cohort studies					
Jones 1994 (antimony metal and antimony trioxide)	No	Yes	Yes	Yes	Moderate
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Schnorr et al. 1995 (antimony oxides)	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Cooper et al. 1968 (antimony trioxide)	No	Yes	Yes	No	Low
Case series					
Potkonjak and Pavlovich 1983 (antimony oxides)	No	Yes	Yes	No	Low
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Cardiovascular effects					
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Outcome: Gastrointestinal effects					
Cohort studies					
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low

Table C-13. Presence of Key Features of Study Design for Antimony—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Case series					
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Developmental effects					
Cohort studies					
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	No	No	Yes	Yes	Low
Case-control studies					
Longerich et al. 1991 (not reported)	No	No	Yes	Yes	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	No	Yes	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	No	Yes	Yes	Moderate
NIOSH 1979 (rat, stibine)	Yes	No	Yes	No	Low
NIOSH 1979 (guinea pig, stibine)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Gross et al. 1952 (rat, antimony trisulfide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Outcome: Cardiovascular effects (myocardium damage or altered EKG)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	Yes	No	Yes	No	Low
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	Yes	No	Yes	No	Low
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	No	Yes	Moderate
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (pigs, antimony trioxide)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Oral acute exposure					
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	No	Yes	Low
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	No	Yes	Moderate
Outcome: Gastrointestinal effects					
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Houpt et al. 1984 (dog, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Metabolic effects (altered blood glucose levels)					
Oral intermediate exposure					
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Oral Chronic exposure					
Schroeder et al. 1970 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral intermediate exposure					
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Studies finding effects		
Inhalation acute exposure		
Animal studies		
Brieger et al. 1954 (rabbit, antimony trisulfide)	Moderate	
NTP 2016 (rat, antimony trioxide)	Moderate	
NTP 2016 (mouse, antimony trioxide)	Moderate	Moderate
NIOSH 1979 (rat, stibine)	Low	
NIOSH 1979 (guinea pig, stibine)	Low	
Inhalation intermediate exposure		
Animal studies		
Belyaeva 1967 (rat, antimony trisulfide)	Moderate	
Brieger et al. 1954 (rat, antimony trisulfide)	Moderate	High
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Low	
Newton et al. 1994 (rat, antimony trioxide)	High	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation chronic exposure		
Human studies		
Renes 1953 (antimony oxides)	Low	
Schnorr et al. 1995 (antimony oxides)	Moderate	
Cooper et al. 1968 (antimony trioxide)	Low	Moderate
Potkonjak and Pavlovich 1983 (antimony oxides)	Low	
Taylor 1966 (antimony trichloride)	Low	
Animal studies		
Gross et al. 1952 (rat, antimony trisulfide)	High	
Groth et al. 1986 (rat, antimony trioxide)	High	
Groth et al. 1986 (rat, antimony ore)	High	
Newton et al. 1994 (rat, antimony trioxide)	High	High
NTP 2016 (rat, antimony trioxide)	High	
NTP 2016 (mouse, antimony trioxide)	High	
Watt 1983 (rat, antimony trioxide)	High	
Watt 1983 (pig, antimony trioxide)	Moderate	
Studies finding no effects		
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954 (antimony trisulfide)	Low	
Jones 1994 (antimony metal and antimony trioxide)	Moderate	Moderate
Outcome: Cardiovascular effects		
Studies finding effects on myocardium and/or EKGs		
Inhalation acute exposure		
Animal studies		
Brieger et al. 1954 (rabbit, antimony trisulfide)	Low	Low
Inhalation intermediate exposure		
Animal studies		
Brieger et al. 1954 (rat, antimony trisulfide)	Moderate	
Brieger et al. 1954 (rabbit, antimony trisulfide)	Low	Moderate
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	Low	
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954 (antimony trisulfide)	Low	Low

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects on myocardium and/or EKGs		
Inhalation intermediate exposure		
Animal studies		
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	Low	Moderate
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Low	
Newton et al. 1994 (rat, antimony trioxide)	Moderate	
Inhalation chronic exposure		
Animal studies		
Groth et al. 1986 (rat, antimony trioxide)	Moderate	Moderate
Groth et al. 1986 (rat, antimony ore)	Moderate	
Newton et al. 1994 (rat, antimony trioxide)	Moderate	
NTP 2016 (rat, antimony trioxide)	Moderate	
NTP 2016 (mouse, antimony trioxide)	Moderate	
Watt 1983 (rat, antimony trioxide)	Moderate	
Watt 1983 (pigs, antimony trioxide)	Low	
Oral acute exposure		
Animal studies		
NTP 1992 (rat, antimony potassium tartrate)	Low	Low
NTP 1992 (mouse, antimony potassium tartrate)	Low	
Oral intermediate exposure		
Animal studies		
Hext et al. 1999 (rat, antimony trioxide)	Moderate	Moderate
Poon et al. 1998 (rat, antimony potassium tartrate)	Moderate	
Outcome: Gastrointestinal effects		
Studies finding effects		
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954	Low	Low
Renes 1953	Low	
Taylor 1966	Low	
Animal studies		
NTP 2016 (mouse, antimony trioxide)	High	High
Oral acute exposure		
Animal studies		
Houpt et al. 1984 (dog, antimony potassium tartrate)	High	High
NTP 1992 (mouse, antimony potassium tartrate)	Moderate	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects		
Inhalation chronic exposure		
Animal studies		
Groth et al. 1986 (rat, antimony trioxide)	High	
Groth et al. 1986 (rat, antimony ore)	High	
NTP 2016 (rat, antimony trioxide)	High	High
Watt 1983 (rat, antimony trioxide)	High	
Watt 1983 (pig, antimony trioxide)	Moderate	
Oral acute exposure		
Animal studies		
NTP 1992 (rat, antimony potassium tartrate)	Moderate	Moderate
Oral intermediate exposure		
Animal studies		
Hext et al. 1999 (rat, antimony trioxide)	High	High
Poon et al. 1998 (rat, antimony potassium tartrate)	High	
Outcome: Metabolic effects		
Studies finding effects on serum glucose levels		
Oral intermediate exposure		
Animal studies		
Poon et al. 1998 (rat, antimony potassium tartrate)	High	High
Oral chronic exposure		
Animal studies		
Schroeder et al. 1970 (rat, antimony potassium tartrate)	High	High
Outcome: Developmental effects		
Studies finding effects		
Inhalation intermediate exposure		
Animal studies		
Belyaeva 1967 (rat, antimony trisulfide)	Moderate	Moderate
Inhalation chronic exposure		
Human studies		
Belyaeva 1967 (metallic antimony, antimony trioxide, antimony pentasulfide)	Low	Low
Oral intermediate exposure		
Animal studies		
Angrisani et al. 1988 (rat, pup CV, antimony trichloride)	High	
Rossi et al. 1987 (rat, pup CV, antimony trichloride)	High	High
Rossi et al. 1987 (rat, antimony trichloride)	High	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects		
Inhalation chronic exposure		
Human studies		
Longerich et al. 1991 (not reported)	Low	Low

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with antimony exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Studies finding effects			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	+1 magnitude, +1 consistency	High
Studies finding no effects			
Human studies	Moderate	-1 risk of bias,	Low
Outcome: Cardiovascular effects			
Studies finding effects on myocardium and/or EKGs			
Human studies	Low	-1 risk of bias,	Very low
Animal studies	Moderate	-1 risk of bias	Low
Studies finding no effects on myocardium and/or EKGs			
Animal studies	Moderate	None	Moderate
Outcome: Gastrointestinal effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Animal studies	High	None	High
Outcome: Metabolic effects			
Studies finding effects on serum glucose levels			
Animal studies	High	None	High
Outcome: Developmental effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Human studies	Low	-1 risk of bias	Very low

Table C-17. Confidence in the Body of Evidence for Antimony

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects		
Effect	Low	High
No effect	Low	No data
Cardiovascular effects		
Effects on myocardium/EKG	Very low	Low
No effect on myocardium/EKG	No data	Moderate
Gastrointestinal effects		
Effect	Very low	High
No effect	No data	High
Metabolic effects		
Effect	No data	High
No effect	No data	No data
Developmental effects		
Effect	Very low	High
No effect	Very low	No data

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for

continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:

- No downgrade if there are no serious imprecisions
- Downgrade one confidence level for serious imprecisions
- Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for antimony, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for antimony is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Antimony

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation only)			
	Low	Health effect	Low
	Low	No effect	Inadequate
Cardiovascular—myocardial and EKG alterations			
	Very Low	Health effect	Inadequate
Gastrointestinal effect			
	Very Low	Health effect	Inadequate
Metabolic—serum glucose alterations			
	No data	–	No data
Developmental effects			
	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation only)			
	High	Health effect	High
Cardiovascular—myocardial and EKG alterations			
	Low	Health effect	Low
	Moderate	No effect	Inadequate

Table C-18. Level of Evidence of Health Effects for Antimony

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Gastrointestinal effects			
	High	Health effect	High
	High	No effect	Evidence of no health effect
Metabolic—serum glucose alterations			
	High	Health effect	High
Developmental effects			
	High	Health effect	High
	No data	–	No data

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

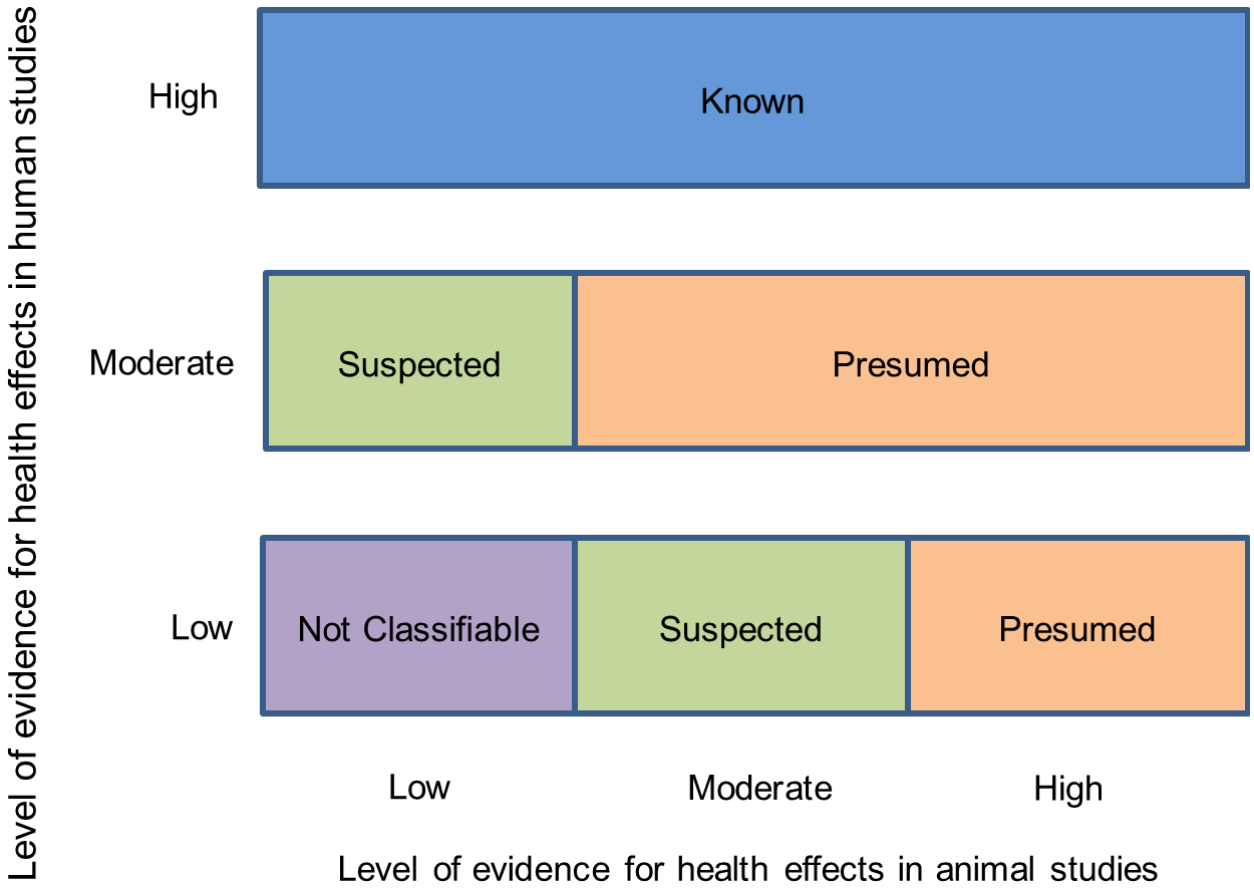
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for antimony are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects following inhalation exposure
  - Low evidence from studies of antimony workers (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995; Taylor 1966).
  - High level of evidence in rats, mice, rabbits, guinea pigs, and pigs from acute exposure to antimony trisulfide, antimony trioxide, and stibine (Brieger et al. 1954; NIOSH 1979; NTP 2016), intermediate exposure to antimony trisulfide and antimony trioxide (Belyaeva 1967; Brieger et al. 1954; Dernehl et al. 1945; Newton et al. 1994), and chronic exposure to antimony trisulfide, antimony trioxide, and antimony ore (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983).
- Gastrointestinal effects
  - Inadequate evidence from studies of antimony workers (Brieger et al. 1954; Renes 1953; Taylor 1966).
  - High level of evidence for gastrointestinal irritation in dogs (Houpt et al. 1984) and mice (NTP 1992, 2016). Inhalation and oral studies in rats with initial confidences of high or moderate did not find histological alterations in the gastrointestinal tract following inhalation exposure to antimony trioxide (Groth et al. 1986; NTP 2016; Watt 1983) or antimony ore (Groth et al. 1986) or oral exposure to antimony trioxide (Hext et al. 1999) or antimony potassium tartrate (NTP 1992; Poon et al. 1998).

Suspected Health Effects

- Cardiovascular-myocardial and EKG alterations
  - Inadequate evidence in humans exposed to antimony trisulfide (Brieger et al. 1954)
  - Low evidence in rats, rabbits, and dogs exposed via inhalation to antimony trisulfide (Brieger et al. 1954) and in rats exposed to antimony potassium tartrate (Schroeder et al. 1970). No myocardial alterations were observed in rat, mouse, pig, or guinea pig antimony ore or antimony trioxide inhalation studies with initial moderate confidence levels (Dernehl et al. 1945; Groth et al. 1986; Newton et al. 1994; Watt 1983) or in antimony trioxide and antimony potassium tartrate oral studies with initial moderate confidence level (Hext et al. 1999; NTP 1992; Poon et al. 1998).
  - Although the hazard identification for myocardial and EKG alterations should be not classifiable based on inadequate evidence in humans and low evidence in animals, the level of the hazard identification was raised to suspected health effect based on consistent evidence of EKG alterations in patients treated with injected trivalent or pentavalent antimony compounds (Dancaster et al. 1966; Honey 1960; Lawn et al. 2006; Neves et al. 2009; Sundar et al. 1998; Thakur 1998) and in animal studies involving parenteral administration (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966).
- Metabolic effect (decreases in blood glucose levels)
  - No data are available on whether inhalation, oral, or dermal exposure to antimony alters blood glucose levels in humans.
  - High evidence in animal studies based on two studies that found decreases in blood glucose levels following intermediate (Poon et al. 1998) or chronic (Schroeder et al. 1970) oral exposure. Decreases in blood glucose levels were also found in rats following repeated intramuscular injection of two organic pentavalent compounds (Alkhawajah et al. 1992b).
  - Based on the high evidence found in the two animal studies, decreases in blood glucose levels should be classified as a presumed health effect. However, because blood glucose levels have only been assessed in two studies administering antimony via

environmentally relevant routes of exposure, the hazard identification was downgraded to suspected health effect.

- Developmental effects
  - Inadequate evidence of developmental effects (decreases in infant growth) from an occupational exposure study (Belyaeva 1967).
  - High evidence of developmental toxicity from animal studies. An inhalation study found decreases in the number of offspring in rats exposed to antimony trioxide during gestation (Belyaeva 1967). An antimony trichloride oral exposure study found decreases in postnatal growth resulting from gestation and lactation exposure, but no effect on the number of offspring or abnormalities (Rossi et al. 1987).
  - Decreases in birth weight and decreases in the number of viable offspring were observed in rat studies involving gestation and/or lactation exposure to subcutaneously administered meglumine antimoniate (Coelho et al. 2014a; Miranda et al. 2006) or intramuscularly administered sodium stibogluconate, meglumine antimoniate, or antimony trichloride (Alkhawajah et al. 1992a).
  - Although the hazard identification for developmental effects, particularly for decreased growth, should be presumed health effect based on inadequate evidence in humans and high evidence in humans, the hazard identification was lowered to suspected health effect based on the small number of studies evaluating the developmental toxicity of antimony by environmentally relevant routes of exposure.

Table C-19. Hazard Identification Conclusions for Antimony

Outcome	Hazard identification
Respiratory effects	Presumed health effect following inhalation exposure
Cardiovascular-myocardial and EKG alterations	Suspected health effect following exposure to soluble antimony compounds
Gastrointestinal effects	Presumed health effect
Metabolic effects (decreased serum glucose levels)	Suspected health effect
Developmental effects	Suspected health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

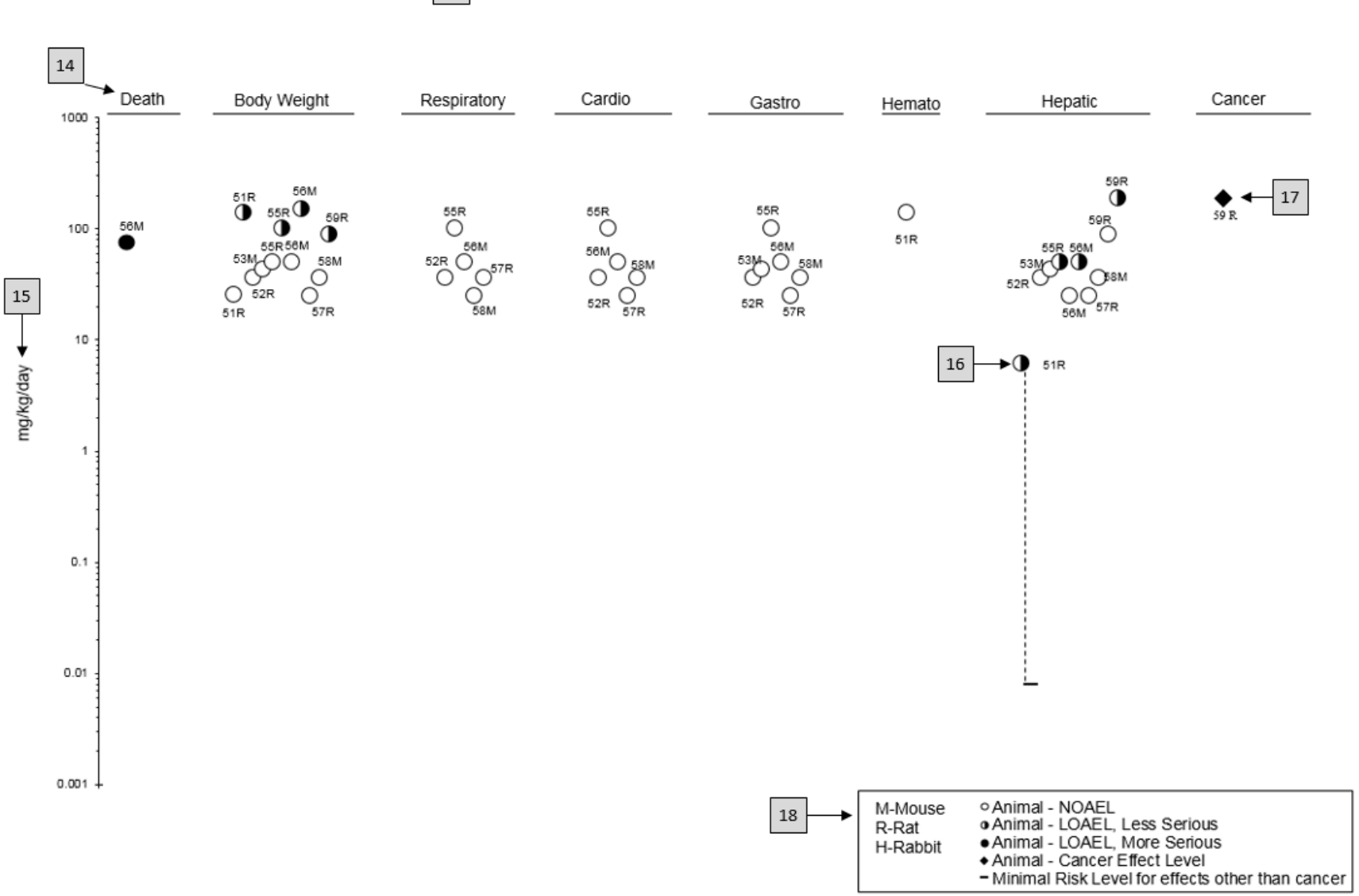
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result