

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.

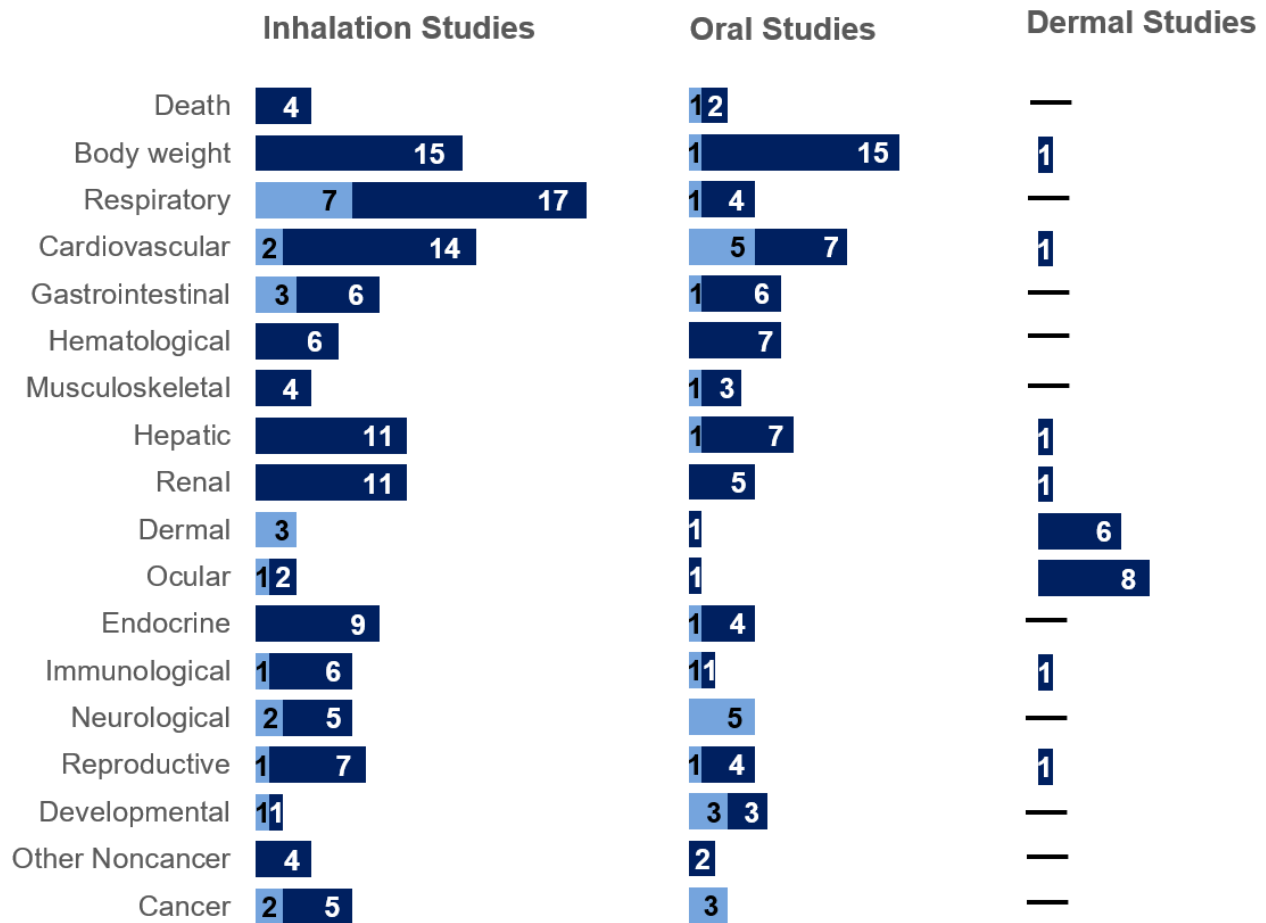
As summarized in Figure 6-1, there are data available on the health effects of antimony in humans and laboratory animals following inhalation, oral, or dermal exposure. Body weight, respiratory tract, and cardiovascular system were the most studied endpoints in animal toxicology studies.

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.

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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

6. ADEQUACY OF THE DATABASE

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 immunoglobulin 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

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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.

6. ADEQUACY OF THE DATABASE

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.