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

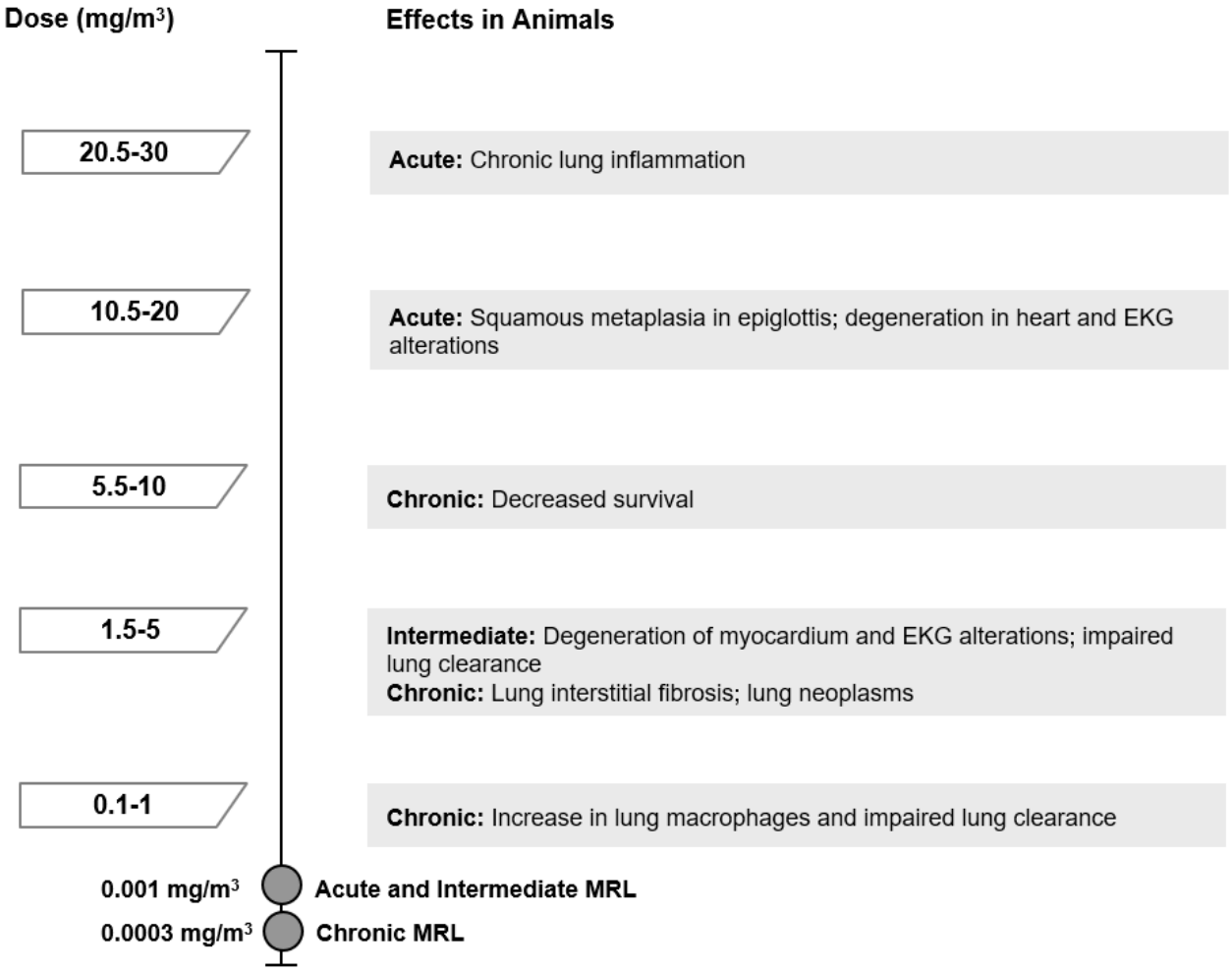
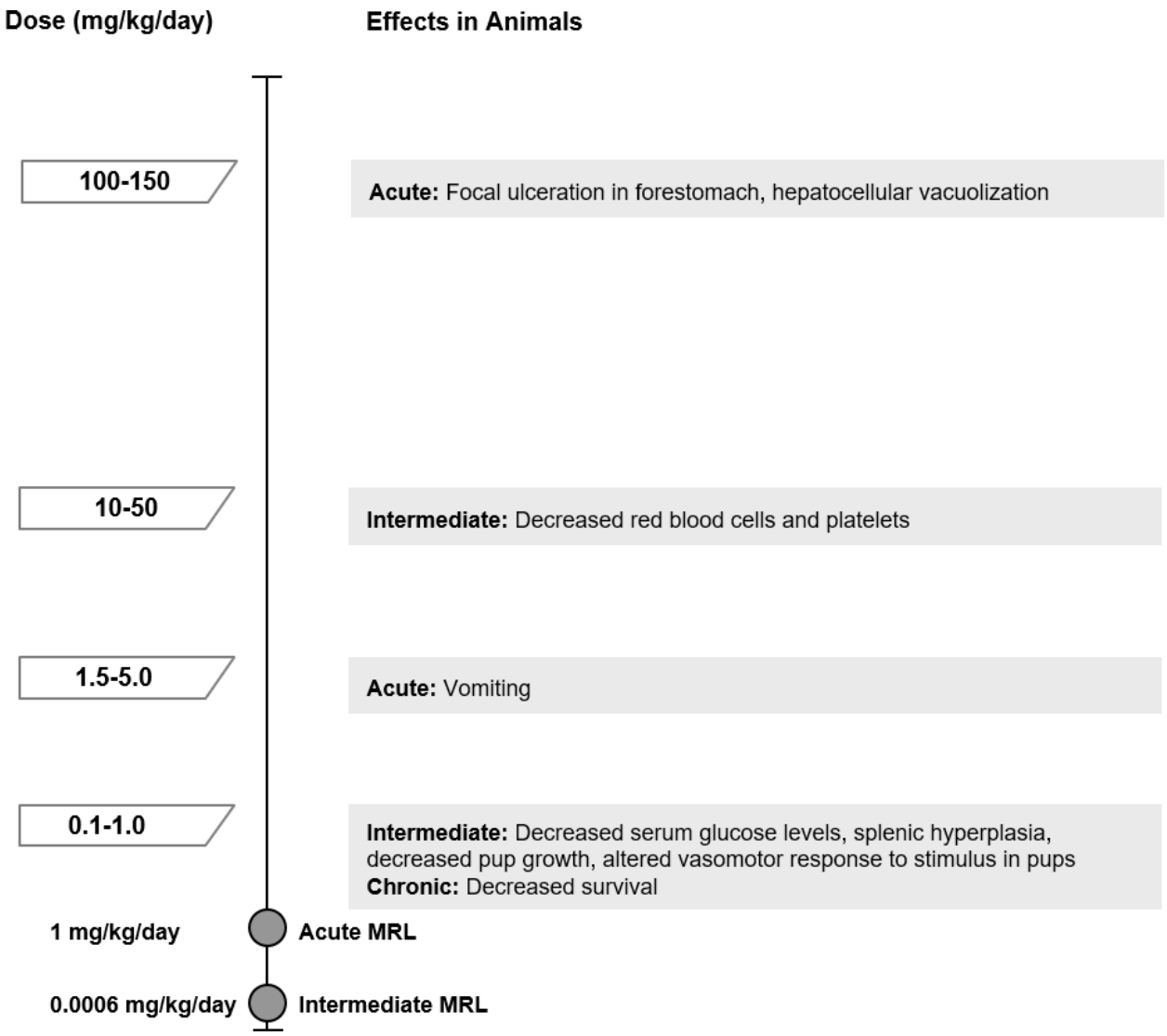


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Antimony



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