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.