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 of the toxicology of antimony and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for antimony based on toxicological studies and epidemiological investigations.

Studies in which humans or animals are exposed to various antimony compounds are discussed in this chapter. The antimony compounds include organic forms (potassium antimony tartrate, sodium antimony tartrate, antimony acetate), inorganic trivalent antimony (antimony trioxide, antimony trichloride, antimony trisulfide, stibine), pentavalent inorganic antimony (antimony pentoxide, antimony pentasulfide), antimony-containing drugs (stibocaptate, stibophen), and metallic antimony. No limitations were placed on the selection of compounds for inclusion in this toxicological profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure

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levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired followLng repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

Health effects have been observed in humans and animals following inhalation exposure to several antimony compounds. Health effects following exposure to airborne stibine, antimony trisulfide, antimony trioxide, antimony pentoxide, antimony trichloride, antimony pentasulfide, and metallic antimony are discussed below. Of these, stibine (antimony hydride) is a naturally occurring gas; for ease of comparison, its concentrations will be expressed in units of mg/m^3 (1 ppm stibine = 5.1 mg/m^3).

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to antimony.

Guinea pigs exposed to approximately 37.9 mg antimony/m^3 as antimony trioxide dust for 52-125 days (Dernehl et al. 1945) or guinea pigs and rats exposed to 1,395 mg antimony/m^3 as stibine gas for 30 minutes (Price et al. 1979) died. In the Dernehl et al. (1945) study, four guinea pigs died, one animal following each of 52, 90, 98, and 125 days of exposure. Pulmonary edema was a contributing factor to the death of rats and guinea pigs exposed to stibine (Price et al. 1979). None of the rats or guinea pigs exposed to 799 mg antimony/m3 for 30 minutes died (Price et al. 1979). Lower concentrations of antimony trisulfide or antimony trioxide did not affect the survival of rats exposed for 1 year (Groth et al. 1986; Wong et al. 1979).

The highest NOAEL values and all reliable LOAEL values for death in each species and duration are presented in Table 2-l and plotted in Figure 2-l.

TABLE 2-1. Levels of Significant Exposure to Antimony - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
ACUTE EXPOSURE								
Death								
1	Rat	30 min		799		1,395 (increased mortality)	Price et al. 1979	Stibine
2	Gn pig	30 min		799		1,395 (increased mortality)	Price et al. 1979	Stibine
Systemic								
3	Rat	30 min	Resp			1,395 (pulmonary edema)	Price et al. 1979	Stibine
			Renal		799 (tubular dilation)			
4	Rabbit	5 d 7 hr/d 5 d/wk	Resp		19.94 (inflammation)		Brieger et al. 1954	Trisulfide
			Cardio			19.94 (myocardial damage altered EKG)		
			Hepatic		19.94 (parenchymatous degeneration)			
			Renal		19.94 (parenchymatous degeneration)			
5	Gn pig	30 min	Resp			1,395 (pulmonary edema)	Price et al. 1979	Stibine
			Renal		799 (tubular dilation)			
INTERMEDIATE EXPOSURE								
Systemic								
6	Rat	13 wk 6 hr/d 5 d/wk	Resp		0.92 (proliferation of macrophages)		Bio/dynamics 1985	Trioxide
			Hemato	19.61				
7	Rat	6 wk 7 hr/d 5 d/wk	Resp		2.20 (congestion)		Brieger et al. 1954	Trisulfide
			Cardio			2.20 (myocardial damage altered EKG)		
8	Rabbit	6 wk 7 hr/d 5 d/wk	Cardio			4.02 (myocardial damage altered EKG)	Brieger et al. 1954	Trisulfide

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
9	Dog	7 wk 7 hr/d 5 d/wk	Cardio	3.81			Brieger et al. 1954	Trisulfide
10	Dog	10 wk 7 hr/d 5 d/wk	Cardio Hemato	 3.98		3.98 (myocardial damage altered EKG)	Brieger et al. 1954	Trisulfide
Developmental								
11	Rat	63-78 d 4 hr/d				209 (decreased number of offspring)	Belyaeva 1967	Trioxide
Reproductive								
12	Rat	63-78 d 4 hr/d				209 (difficulty conceiving)	Belyaeva 1967	Trioxide
CHRONIC EXPOSURE								
Death								
13	Rat	52 wk 7 hr/d 5 d/wk		17.48			Groth et al. 1986; Wong et al. 1979	Trisulfide
14	Rat	52 wk 7 hr/d 5 d/wk		36			Groth et al. 1986; Wong et al. 1979	Trioxide
Systemic								
15	Human	9-31 yr	Resp Resp		8.87 (pneumoconiosis) 8.87 (upper airway inflammation)		Potkonjak and Pavlovich 1983	Trioxide and pentoxide
16	Human	8 mo-2 yr 8 hr/d 5 d/wk	Cardio Gastro			2.15 (altered EKG, elevated blood pressure) 2.15 (ulcer)	Brieger et al. 1954	Trisulfide

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
17	Rat	12 mo 6 hr/d 5 d/wk	Resp Gastro Musc/skel	 4.2 4.2		1.6 (focal fibrosis)	Watt 1980	Trioxide
18	Rat	1 yr 6 hr/d 5 d/wk	Resp Hemato Other	 4.01 	0.07 (chronic inflammation and proliferation of macrophages) 0.07 (hyperplasia in peribronchiolar lymph nodes)	4.01 (fibrosis)	Bio/dynamics 1990	Trioxide
19	Rat	14.5 mo 25 hr/wk	Resp			83.6 (lipoid pneumonia)	Gross et al. 1952	Trioxide
Systemic								
20	Rat	52 wk 7 hr/d 5 d/wk	Resp Cardio Hepatic Renal	 36 36 36		36 (interstitial fibrosis)	Groth et al. 1986; Wong et al. 1979	Trioxide
21	Rat	52 wk 7 hr/d 5 d/wk	Resp Cardio Hepatic Renal	 17.48 17.48 17.48		17.48 (interstitial fibrosis)	Groth et al. 1986; Wong et al. 1979	Trisulfide
22	Rat	1 yr 6 hr/d 5 d/wk	Resp Hemato	 4.2		1.6 (focal fibrosis)	Watt 1983	Trioxide
23	Pig	1 yr 6 hr/d 5 d/wk	Resp Cardio Hemato	4.2 4.2 4.2			Watt 1983	Trioxide

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (mg/m^3)	LOAEL (effect) Less serious (mg/m^3)	LOAEL (effect) Serious (mg/m^3)	Reference	Form
Cancer								
24	Rat	1 yr 6 hr/d 5 d/wk				4.2 (CEL-lung neoplasms)	Watt 1983	Trioxide
25	Rat	52 wk 7 hr/d 5 d/wk				36 (CEL-lung tumor)	Groth et al. 1986; Wong et al. 1979	Trioxide
26	Rat	52 wk 7 hr/d 5 d/wk				17.48 (CEL-lung tumors)	Groth et al. 1986; Wong et al. 1979	Trisulfide

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; CEL = cancer effect level; d = day; EKG = electrocardiogram; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; min = minute; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; yr = year

FIGURE 2-1. Levels of Significant Exposure to Antimony - Inhalation

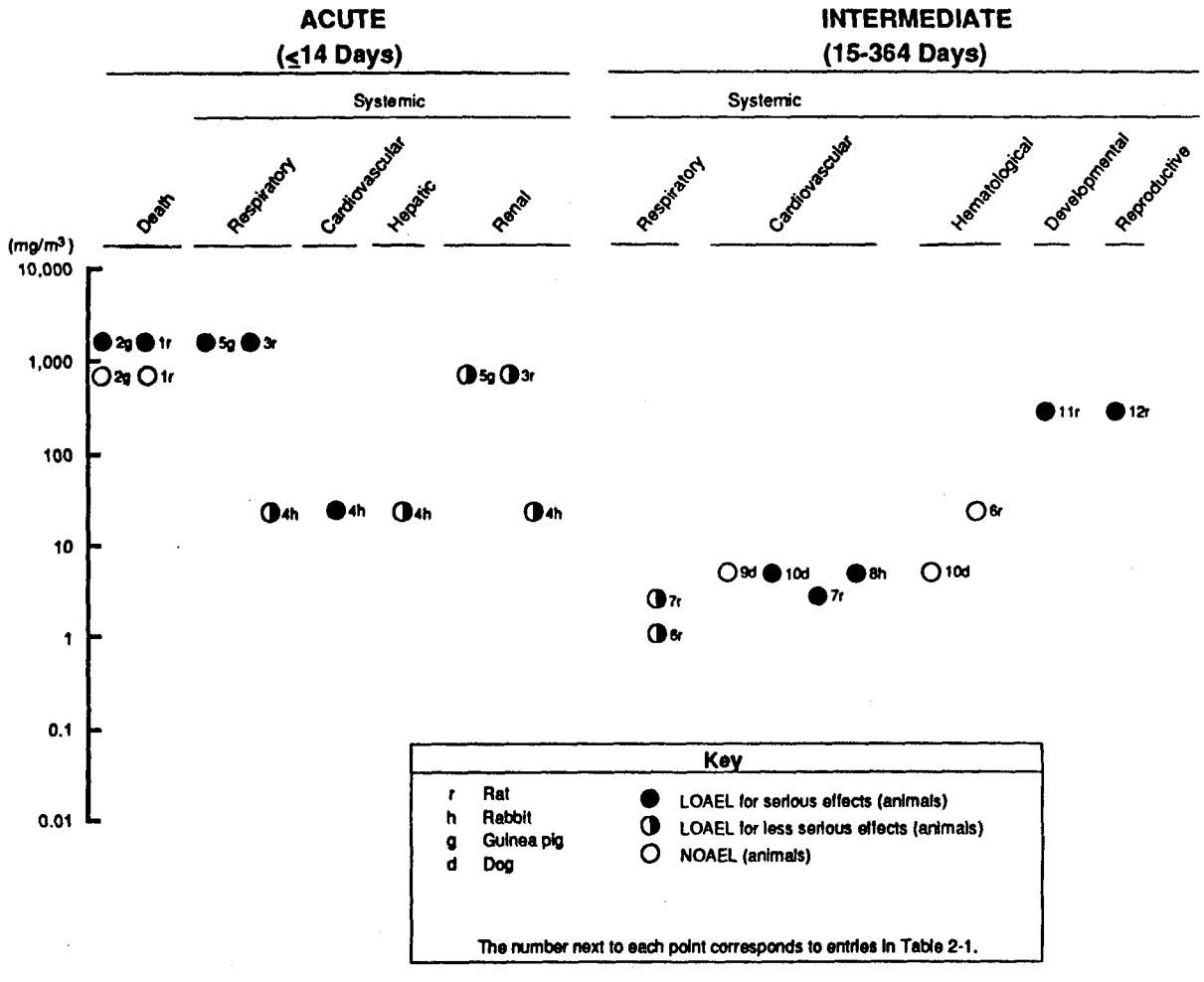
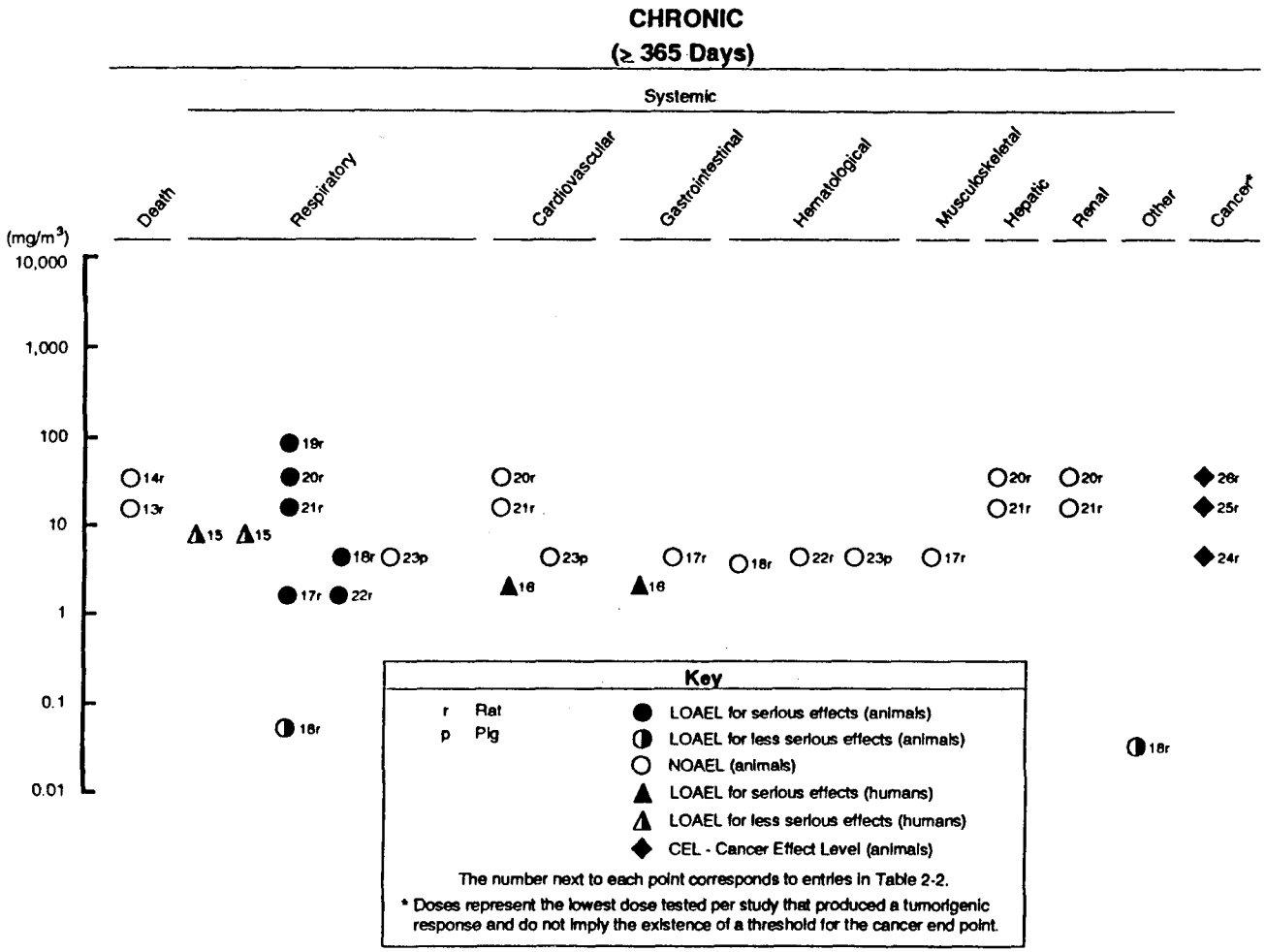


FIGURE 2-1 (Continued)



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2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration are presented in Table 2-l and plotted in Figure 2-1.

Respiratory Effects. Occupational exposure to antimony trioxide and/or pentoxide dust (8.87 mg antimony/m^3 or greater) resulted in antimony pneumoconiosis (inflammation of the lungs due to the irritation caused by the inhalation of dust) (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953). Alterations in pulmonary function (airway obstruction, bronchospasm, and hyperinflation) have been reported in workers exposed to airborne antimony (Cooper et al. 1968; Potkonjak and Pavlovich 1983). Other respiratory effects reported in workers include chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions, and irritation (Potkonjak and Pavlovich 1983). The respiratory irritation reported in the workers diagnosed as having pneumoconiosis was characterized by chronic coughing, wheezing, and upper airway inflammation. Respiratory irritation was not noted in workers exposed to antimony trisulfide for 8 months to 2 years (Brieger et al. 1954). In the reports of health effects associated with occupational exposure to antimony, the workers inhaled a variety of compounds including antimony pentoxide, arsenic oxide, iron oxide, hydrogen sulfide, and sodium hydroxide (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953).

A variety of respiratory effects have been reported in animals exposed to antimony. A majority of these effects are associated with the physiological response to dust accumulation in the lung (pneumoconiosis). The effects progress from pneumoconiosis and a proliferation of alveolar macrophages to fibrosis.

Lung inflammation was noted in rabbits exposed to antimony trisulfide for 5 days (Brieger et al. 1954).

Acute exposure to stibine gas also results in lung effects. Pulmonary edema was observed in rats and guinea pigs exposed to a lethal concentration of stibine for 30 minutes (Price et al. 1979).

A dose-related increase in the number of alveolar and/or intraalveolar macrophages was observed in rats exposed to antimony trioxide for 13 weeks or more (Bio/dynamics 1985, 1990). In rats exposed to 0.07 mg antimony/m^3 for 1 year or to 0.92 mg antimony/m^3 for 13 weeks, the proliferation of macrophages was still present for 12 months or 28 weeks, respectively, after exposure termination (Bio/dynamics 1985, 1990). Chronic interstitial inflammation was also observed in rats exposed to 0.07 mg antimony/m^3 for 1 year with a 1 year recovery.

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The proliferation of macrophages is a normal physiological response to the deposition of insoluble particulates in the lung. However, excessive phagocytic activity prompted by extensive or repeated deposition of particulates in the lung probably contributes to the development of fibrosis. Because of the integral role the macrophages have in the progression to fibrosis, nonreversible proliferation of macrophages is considered a less serious adverse health effect.

More severe respiratory effects have also been reported in animals exposed to antimony. Interstitial fibrosis and lipoid pneumonia have been observed in rats exposed to antimony trisulfide or antimony trioxide for 1 year (Bio/dynamics 1990; Gross et al. 1952; Groth et al. 1986; Watt 1980, 1983; Wong et al. 1979). These effects have been reported at exposure levels between 1.6 and 83.6 mg antimony/m^3. No respiratory effects were reported in pigs exposed to 4.2 mg antimony/m^3 as antimony trioxide for 1 year (Watt 1983).

Cardiovascular Effects. Increased blood pressure (greater than 150/90) and altered EKG readings were observed in workers exposed to 2.15 mg antimony/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 another group of antimony workers, one out of seven had altered EKG readings (Renes 1953). These limited data on cardiovascular effects in humans are supported by the finding of cardiac effects following parenteral administration of antimony to humans (see discussion of systemic effects in Section 2.4).

Inhalation exposure to antimony trisulfide dust (the same dust the factory workers were exposed to) 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 19.94 mg antimony/m^3 as antimony trisulfide resulted in EKG alterations in rabbits. The effective exposure levels resulting in cardiovascular effects were at least four times lower (2-4 mg antimony/m^3) in rats, rabbits, and dogs exposed to airborne antimony for 6-10 weeks, as compared to rabbits acutely exposed (Brieger et al. 1954). Dogs exposed to 3.81 mg antimony/m^3 as antimony trisulfide for 7 weeks (Brieger et al. 1954) or pigs exposed to 4.2 mg antimony/m^3 as antimony trioxide for 1 year (Watt 1983) did not exhibit changes in EKG readings. The degenerative changes of the myocardium observed in rats, rabbits, and dogs exposed to antimony trisulfide consisted of hyperemia and swelling of myocardial fibers (Brieger et al. 1954). Myocardial damage was not observed in rats exposed to 17.48 mg antimony/m^3 as antimony trioxide for 1 year (Groth et al. 1986; Watt 1980; Wong et al. 1979).

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Gastrointestinal Effects. A variety of gastrointestinal disorders have occurred in factory workers engaged in activities including repeated prolonged exposure to airborne antimony trichloride (Taylor 1966), antimony trisulfide (Brieger et al. 1954) or antimony oxide (Renes 1953). These disorders 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). 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 antimony/m^3.

Symptoms of gastrointestinal disturbances were not reported in animals, and no histopathological alterations were observed in rats exposed to antimony trioxide (4.2 mg antimony/m^3) for 1 year (Watt 1980).

Hematological Effects. No studies were located regarding hematological effects in humans after inhalation exposure to antimony.

Toxicologically significant hematological effects have not been observed in rats and pigs following long-term exposure to antimony aerosols ranging from 4 to 20 mg antimony/m^3 as antimony trioxide (Bio/dynamics 1985, 1990; Watt 1983). The only effects observed were small (but statistically significant) changes in the hemoglobin concentration in the erythrocytes and erythrocyte volume in rats exposed to 4.01 mg antimony/m^3 as antimony trioxide (Bio/dynamics 1990).

Musculoskeletal Effects. 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 antimony/m^3 as antimony trioxide for 1 year (Watt 1980).

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to antimony.

Parenchymatous and fatty degeneration was observed in rabbits exposed to 19.94 mg antimony/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954) and in guinea pigs exposed to 37.9 mg antimony/m^3 as antimony trioxide for 30 weeks (Dernehl et al. 1945). The duration of exposure is unclear in the Dernehl et al. (1945) study. No hepatic effects were observed in rats exposed to antimony trioxide for 13 weeks (Bio/dynamics 1985) or after 1 year of exposure to antimony trioxide or antimony trisulfide concentrations of 36 mg antimony/m^3 or lower (Bio/dynamics 1990; Groth et al. 1986; Watt 1980; Wong et al. 1979).

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Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to antimony.

Tubular dilation was observed in rats and guinea pigs exposed to stibine gas for 30 minutes at a concentration of 799 mg antimony/m^3 (Price et al. 1979). Parenchymatous degeneration was observed in rabbits exposed to 19.94 mg antimony/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954). No renal effects were noted in rats exposed to 19.6 mg antimony/m^3 as antimony trioxide for 13 weeks (Bio/dynamics 1985) or 17.5 mg antimony/m^3 as antimony trisulfide or up to 36 mg antimony/m^3 as antimony trioxide for 1 year (Bio/dynamics 1990; Groth et al. 1986; Wong et al. 1979).

Dermal/Ocular Effects. Dermal and ocular effects have been reported in humans. and animals. These effects (ocular conjunctivitis and dermatosis) result from airborne antimony coming into contact with the skin and/or eyes (Potkonjak and Pavlovich 1983; Renes 1953; Stevenson 1965).

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 2.2.3.3).

Eye irritation has been observed in rats and guinea pigs exposed to stibine gas (Price et al. 1979) and antimony trioxide (Bio/dynamics 1985). Cataracts and chromodacryorrhea have been observed in rats exposed to antimony trioxide for 1 year with a 1 year recovery period (Bio/dynamics 1990). The authors suggest that the chromodacryorrhea may have been secondary to dental abnormality, infectious disease, or xerosis.

Because these dermal and ocular effects may not be the result of inhalation exposure, but rather dermal contact with airborne antimony, the LOAEL values were not recorded in Table 2-l or Figure 2-l. Alopecia was noted in rats exposed to 0.92 mg antimony/m^3 or greater as antimony trioxide for 13 weeks (Bio/dynamics 1985). Because high levels of antimony are measured in the skin or hair of animals following nose-only exposure to antimony aerosols, this effect may not be the result of dermal contact to airborne antimony (Felicetti et al. 1974a, 1974b).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to antimony. Hyperplasia

of the reticuloendothelial cells in the peribronchiolar lymph nodes was observed in rats exposed to 0.07 mg antimony/m^3 antimony trioxide for 1 year with a 1 year recovery period (Bio/dynamic 1990).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to antimony.

2.2.1.4 Neurological Effects

A causal relationship between exposure to airborne antimony and neurological effects in humans has not been established. Nerve tenderness and a tingling sensation were reported in workers exposed to antimony oxide at a concentration of 10.07 mg antimony/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.

No studies were located regarding neurological effects in animals after inhalation exposure to antimony.

2.2.1.5 Developmental Effects

An increased incidence of spontaneous abortions, compared to a control grow, were reported in women working at an antimony metallurgical plant. The women were exposed to a mixture of antimony trioxide, antimony pentasulfide, and metallic antimony (Belyaeva 1967). The level of airborne antimony and presence of other compounds is not known. In addition, a description of the control group was not given; thus, it is unclear if the controls had jobs comparable to those of the exposed group.

A decreased number of offspring was born to rats exposed to 209 mg antimony/m^3 as antimony trioxide prior to conception and throughout gestation. No difference in fetal body weights was observed (Belyaeva 1967). This LOAEL for developmental effects in rats is presented in Table 2-l and Figure 2-1.

2.2.1.6 Reproductive Effects

Disturbances in the menstrual cycle were reported in women exposed to airborne metallic antimony, antimony pentasulfide, and antimony trioxide in a metallurgical plant. No other details were provided (Belyaeva 1967).

In rats exposed to 209 mg antimony/m3 as antimony trioxide for 63 days, 67% failed to conceive. Metaplasia in the uterus and disturbances in the ovum-maturing process were obsewed in the animals that failed to conceive,. These effects were not observed in the rats that conceived (Belyaeva 1967).

This LOAEL value for reproductive effects in rats is presented in Table 2-l and Figure 2-l.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to antimony.

Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

Inhalation exposure to 8.87 mg antimony/m^3 as antimony oxide did not affect the incidence of cancer in workers employed for 9-31 years (Potkonjak and Pavlovich 1983).

Antimony can be carcinogenic in rats. Lung tumors were observed in rats exposed to 4.2 or 36 mg antimony/m3 as antimony trioxide (Groth et al. 1986; Watt 1980, 1983; Wong et al. 1979) or 17.48 mg antimony/m^3 as antimony trisulfide for 1 year (Groth et al. 1986; Wong et al. 1979). An increased incidence of lung tumors was not observed in rats exposed to 4.01 mg antimony/m^3 as antimony trioxide (Bio/dynamics 1990) or in pigs exposed to 4.2 mg antimony/m^3 as antimony trioxide (Watt 1983). The carcinogenic potential of antimony may be related to the deposition and clearance of antimony from the respiratory tract. Further discussion is presented in Section 2.4. The cancer effect levels are recorded in Table 2-1 and Figure 2-l.

2.2.2 Oral Exposure

Health effects have been observed in humans and animals following oral exposure to a variety of antimony compounds. Adverse effects following exposure to potassium antimony tartrate (an organic form of antimony), antimony trichloride, antimony trioxide, and metallic antimony are discussed below.

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to antimony.

Mortality was not observed in rats following a single exposure to 188-16,714 mg antimony/kg or lower as inorganic antimony (Fleming 1982; Myers et al. 1978; Smyth and Carpenter 1948; Smyth and Thompson 1945) or to a 7,000 mg antimony/kg dose of metallic antimony (Bradley and Frederick 1941). However, a lower single dose of organic antimony (300 mg antimony/kg dose as potassium antimony tartrate) resulted in death in rats (Bradley and Frederick 1941). Death was attributed to myocardial failure. These NOAELS and LOAELs

for death in animals suggest that organic antimony is more lethal than the inorganic compounds, probably due to increased absorption of the potassium antimony tartrate.

Chronic administration of a low dose of potassium antimony tartrate (0.262 mg antimony/kg/day) resulted in decreased lifespan in rats (Schroeder et al. 1970). No effect on longevity was observed in mice exposed to 0.35 mg antimony/kg/day as potassium antimony tartrate (Kanisawa and Schroeder 1969; Schroeder et al. 1968).

The highest NOAEL values for each antimony compound and all reliable LGAEL values are presented in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

Cardiovascular, gastrointestinal, hematological, hepatic, and other systemic effects observed following oral exposure to antimony are presented below. No studies were located regarding respiratory, musculoskeletal, renal, or dermal/ocular effects in human and animals after oral exposure to antimony. The highest NOAEL values and all reliable LOAELs for each systemic effect in each species and duration are presented in Table 2-2 and plotted in Figure 2-2.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to antimony. No effect on blood pressure or heart rate was observed in rats exposed to antimony as antimony trichloride (Marmo et al. 1987) or antimony trioxide (Gross et al. 1955). Pre- and postnatal exposure or only postnatal exposure alone to 0.0748 mg antimony/kg/day as antimony trichloride appears to affect the development of certain cardiovascular reflexes in rats that are important for regulating systemic arterial blood pressure. In rats exposed to antimony trichloride pre- and postnatally or postnatally, a decreased pressor response to 1-noradrenaline and a decreased hypotensive response to 1-isoprenaline and acetylcholine was observed (Marmo et al. 1987). The occurrence of the effect is duration related.

Gastrointestinal Effects. Shortly after drinking an average of 10 ounces of lemonade contaminated with potassium antimony tartrate (equivalent to 0.53 mg antimony/kg for a 70 kg man), workers began to vomit (Dunn 1928). Gastrointestinal effects have also been reported in factory workers after exposure to airborne antimony dust. As discussed in Section 2.2.1.2, the gastrointestinal effects probably resulted from swallowing the antimony dust.

Vomiting and diarrhea have also been observed in animals following acute exposure to antimony trioxide or potassium antimony tartrate (Houpt et al.

TABLE 2-2. Levels of Significant Exposure to Antimony - Oral

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Rat	(GW)	1 d 1x/d				300 (decreased survival)	Bradley and Frederick 1941	Potassium tartrate
2	Rat	(GO)	1 d 1x/d		7,000			Bradley and Frederick 1941	Metallic antimony
3	Rat	(F)	1 d 1x/d		16,714			Smyth and Thompson 1945	Trioxide
Systemic									
4	Human	(W)	1 d	Gastro		0.529 (vomiting)		Dunn 1928	Potassium tartrate
5	Rat	(GO)	1 d 1x/d	Gastro		16,714 (diarrhea)		Myers et al. 1978	Trioxide
6	Rat	(GW)	1 d 1x/d	Gastro Hepatic	376 376			Fleming 1982	Trioxide
7	Dog	(W)	1 d	Gastro		13.2 (vomiting)		Houpt et al. 1984	Potassium tartrate
INTERMEDIATE EXPOSURE									
Systemic									
8	Rat	(F)	24 wk	Hemato	500	1,000 (decreased hemotocrit and hemoglobin)		Sunagawa 1981	Metallic antimony
				Hepatic	250	500 (cloudy swelling in hepatic cords)			
9	Rat	(F)	12 wk	Hemato	418			Hiraoka 1986	Trioxide

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
10	Rat	(W)	30 d	Cardio	0.0748	0.748 (decreased hypotensive response in newborns)		Marmo et al. 1987	Trichloride
11	Rat	(F)	24 wk	Hemato		418 (decreased RBC count)		Sunagawa 1981	Trioxide
				Hepatic		418 (cloudy swelling in hepatic cords)			
12	Rat	(F)	12 wk	Hemato		500 (decreased total plasma protein)		Hiraoka 1986	Metallic antimony
13	Rat	(GW)	20 d 1x/d	Gastro	501			Fleming 1982	Trioxide
14	Rat	(W)	81 d Gd 0-21 birth to 60 days	Cardio		0.0748 (decreased hypotensive response in newborns)		Angrisani 1988; Marmo et al. 1987; Rossi et al. 1987	Trichloride
15	Rat	(W)	60 d	Cardio		0.0748 (decreased hypotensive response in newborns)		Marmo et al. 1987	Trichloride
16	Rat	(W)	21 d Gd 0-21	Other		0.0748 (decreased maternal weight gain)		Rossi et al. 1987	Trichloride
17	Rat	(F)	30 d	Hemato	226	894 (increased RBC count)		Smyth and Thompson 1945	Trioxide
18	Dog	(GW)	32 d 1x/d	Gastro			84 (severe diarrhea)	Fleming 1982	Trioxide
				Other			6,644 (weight loss)		
Neurological									
19	Dog	(GW)	32 d 1x/d				6,644 (muscle weakness)	Fleming 1982	Trioxide

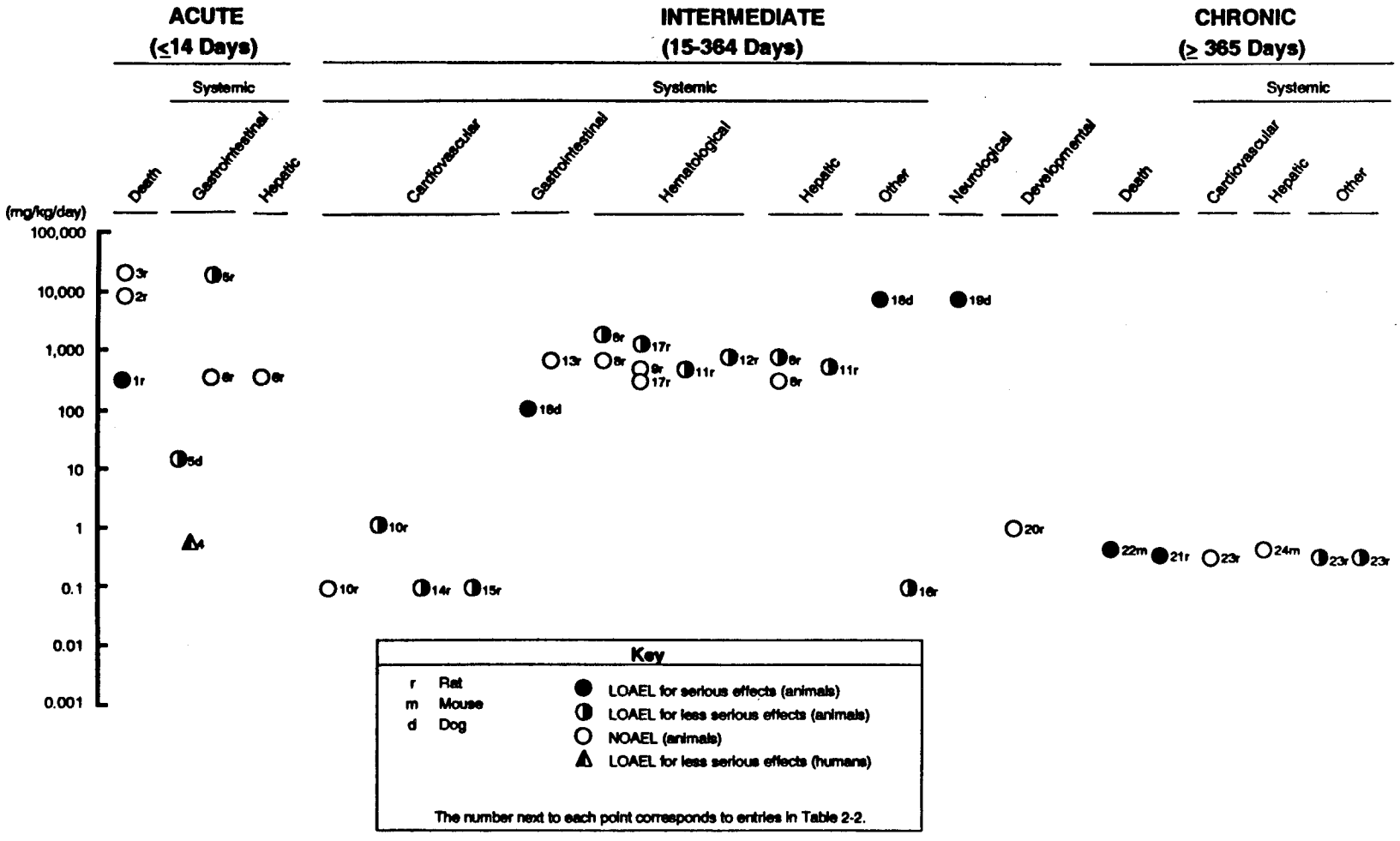
TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference	Form
Developmental									
20	Rat	(W)	21 d Gd 0-21		0.748			Rossi et al. 1987	Trichloride
CHRONIC EXPOSURE									
Death									
21	Rat	(W)	746-1,342 d				0.262 (decreased lifespan)	Schroeder et al. 1970	Potassium tartrate
22	Mouse	(W)	542-909 d				0.35 (decreased lifespan - females)	Kanisawa and Schroeder 1969; Schroeder 1968	Potassium tartrate
Systemic									
23	Rat	(W)	746-1,342 d	Cardio	0.262			Schroeder et al. 1970	Potassium tartrate
				Other		0.262 (decreased nonfasting serum glucose)			
				Other		0.262 (increased serum cholesterol)			
24	Mouse	(W)	542-909 d	Hepatic	0.35			Schroeder et al. 1968	Potassium tartrate

[a]The number corresponds to entries in Figure 2-1.

Cardio = cardiovascular; d = day; (F) = food; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage oil; (GW) = gavage water; Hemato = hematological; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; (W) = water; wk = week

FIGURE 2-2. Levels of Significant Exposure to Antimony - Oral



1984; Myers et al. 1978). Severe diarrhea was observed in dogs administered 84 mg antimony/kg/day as antimony trioxide for 32 days. No gastrointestinal effects or gross abnormalities were noted in rats exposed to 501 mg antimony/kg/day or less as antimony trioxide for 20 days (Fleming 1982).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to antimony.

Mild hematological alterations are observed in animals exposed to 418 mg antimony/kg/day or greater. Increased red blood cell count was observed in rats exposed to 894 mg antimony/kg/day as antimony trioxide for 30 days (Smyth and Thompson 1945). Exposure to metallic antimony resulted in decreased hematocrit and hemoglobin levels and decreased plasma protein levels in rats exposed to 500-1,000 mg antimony/kg/day for 12-24 weeks (Hiraoka 1986; Sunagawa 1981). Decreased red blood cell count was observed in rats exposed to 418 mg antimony/kg/day as antimony trioxide for 24 weeks (Sunagawa 1981).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to antimony.

Cloudy swelling of the hepatic cords has been observed in rats exposed to 418 mg antimony/kg/day as antimony trioxide or 500 mg antimony/kg/day as metallic antimony (Sunagawa 1981). Hepatic effects have not been observed at lower concentrations of antimony trioxide or potassium antimony tartrate (Fleming 1982; Schroeder et al. 1968).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to antimony.

Severe weight loss was observed in dogs administered 6,644 mg antimony/kg/day as antimony trioxide. Severe diarrhea and vomiting were also observed in these dogs (Fleming 1982).

Increased serum cholesterol and decreased nonfasting serum glucose levels were observed in rats exposed for a lifetime to low levels of potassium antimony tartrate in drinking water (Schroeder et al. 1970). The toxicologic significance of these effects is not known.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans or animals after oral exposure to antimony.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to antimony.

Muscle weakness and difficulty in moving hind limbs were observed in a dog exposed to 6,644 mg antimony/kg/day as antimony trioxide for 32 days (Fleming 1982). This LOAEL value for neurological effects in dogs is recorded in Table 2-2 and Figure 2-2.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to antimony.

No developmental effects (differences in the number of newborn pups per litter and macroscopic teratogenic effects) were observed in the offspring of rats treated during gestation with 0.748 mg antimony/kg/day as antimony trichloride (Rossi et al. 1987). As discussed in the cardiovascular effects section, pre- and postnatal or postnatal exposure impaired the development of certain cardiovascular reflexes that are important in regulating systemic arterial blood pressure (Angrisani et al. 1988; Marmo et al. 1987; Rossi et al. 1987). Because comparisons were not made between the hypotensive response in pups exposed prenatally and the response in pups exposed postnatally, the potential of antimony trichloride to produce developmental cardiovascular effects cannot be assessed.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after oral exposure to antimony.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to antimony.

Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans after oral exposure to antimony.

No change in the incidence of cancer was observed in rats (Schroeder 1970) or mice (Kanisawa and Schroeder 1969; Schroeder 1968) fed 0.262 or 0.35 mg antimony/kg/day, respectively, as potassium antimony tartrate 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.

2. HEALTH EFFECTS

2.2.3 Dermal Exposure

The dermal toxicity of antimony compounds is discussed below. Data were located on the health effects following application of antimony trioxide, antimony thioantimonate (a mixture of antimony trfsulfide, and antimony pentasulfide) and antimony oxide to the skin or eye.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to antimony.

Death was observed in rabbits following a single application of antimony oxides at a level of 6,685 mg antimony/kg (Myers et al. 1978). The cause of death was not reported. Two out of four rabbits died after 6-8 topical applications of antimony trioxide paste. The antimony trioxide was combined with a mixture formulated to resemble acidic sweat. The application area was not occluded; thus, there is a possibility of oral ingestion of the paste (Fleming 1982). Death was not reported in rabbits after 13 weeks of application of a 5% solution of antimony thioantimonate (a mixture of antimony trisulfide and antimony pentasulfide) (Horton et al. 1986). The highest NOAEL and all reliable LOAEL values for death for rabbits for each duration are recorded in Table 2-3.

2.2.3.2 Systemic Effects

Respiratory, cardiovascular, gastrointestinal, and dermal/ocular effects following dermal or ocular exposure are presented below. No studies were located regarding respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans and animals following dermal exposure to antimony. The highest NOAEL for each antimony compound and all reliable LOAEL values for each systemic effect for each species are recorded in Table 2-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to antimony. Hyperemia in the lungs was observed in two rabbits that died after 6-8 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, 1982). The application area was not occluded; thus, the ingestion of the paste may have occurred.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following dermal exposure to antimony. Application of a 5% solution of antimony thioantimonate did not change EKG readings or heart pathology in rabbits (Horton et al. 1986).

TABLE 2-3. Levels of Significant Exposure to Antimony - Dermal

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Form
ACUTE EXPOSURE							
Death							
Rabbit	1 d				6,685 mg/kg (1/6 died)	Myers et al. 1978	Trioxide
Systemic							
Rabbit	1 d 1x/d	Ocular		79.2 mg (mild eye irritation)		Wil Research Laboratories 1979	Oxide
Rabbit	1 d 1x/d	Ocular		100 mg (eye irritation)		Horton et al. 1986	Trisulfide and pentasulfide
Rabbit	1 d	Dermal		6,685 mg/kg (edema)		Myers et al. 1978	Trioxide
Rabbit	1 d 1x/d	Ocular	209 mg			Myers et al. 1978	Trioxide
Rabbit	1 d 1x/d	Dermal	20,900 mg			Gross et al. 1955	Trioxide
Neurological							
Rabbit	1 d			6,685 mg/kg (abnormal gait)		Myers et al. 1978	Trioxide
INTERMEDIATE EXPOSURE							
Death							
Rabbit	13 wk 5 d/wk		5%			Horton et al. 1986	Trisulfide and pentasulfide

TABLE 2-3 (Continued)

Species	Exposure frequency/ duration	System	NOAEL	LOAEL (effect)		Reference	Form
				Less serious	Serious		
Systemic							
Rabbit	13 wk 5 d/wk	Cardio Derm/oc Other	5% 5% 5%			Horton et al. 1986	Trisulfide and pentasulfide

Cardio = cardiovascular; d = day; Derm/oc = dermal/ocular; Gn pig = guinea pig; hr = hour; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week

Gastrointestinal Effects. 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 two rabbits that died after 6-8 applications of an antimony trioxide-acidic sweat paste (Fleming 1982). Because the application area was not occluded, ingestion of the paste is possible.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans following dermal exposure to antimony.

In rabbits, edema was noted in the area where an antimony trioxide patch (6,685 mg antimony/kg) was applied for 1 day (Myers et al. 1978).

Instillation of 79-100 mg antimony.as antimony oxide or antimony thioantimonate into the eyes of rabbits resulted in eye irritation (Horton et al. 1986; Wil Research Laboratories). However, instillation of antimony trioxide (34.5-83.6 mg antimony) did not result in eye irritation (Gross et al. 1955; Myers et al. 1978).

Dermal and ocular effects have been observed in humans and animals exposed to airborne antimony. The effects include ocular onjunctivitis, eye irritation, and dermatosis. Further information on these effects is provided in Section 2.2.1.2.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans and animals following dermal exposure to antimony.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to antimony.

Abnormal gait was observed in rabbits following application of a lethal concentration of antimony trioxide (6,685 mg antimony/kg/day) (Myers et al. 1978). This LOAEL value for neurotoxicity in rabbits is recorded in Table 2-3.

No studies were located regarding the following effects in humans or animals after dermal exposure to antimony:

2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2. HEALTH EFFECTS

2.2.3.8 Cancer

No studies were located regarding cancer effects in humans or animals after dermal exposure to antimony.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Quantitative data on the absorption of antimony from the lungs in humans were not located. Elevated blood and urine antimony levels were observed in workers exposed to antimony, suggesting that antimony is absorbed (Cooper et al. 1968; Ludersdorf et al. 1987). However, there is a possibility that some of the antimony detected in the urine and blood was swallowed.

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-time of some forms of antimony in the lungs may be longer than weeks (Gerhardsson et al. 1982).

The absorption of antimony from the respiratory tract is a function of particle size. Exposure to antimony tartrate with a particle size of 1.6 μm 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 difference in the body burden, 1 day after exposure to trivalent or pentavalent antimony tartrate, was observed (Felicetti et al. 1974b). Although no information on differences in absorption rates between antimony compounds was located, differences related to solubility probably exist.

2.3.1.2 Oral Exposure

No quantitative data on the absorption of antimony from the gastrointestinal tract in humans were located. However, results of studies in animals suggest that at least certain forms of antimony are probably 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), suggesting that absorption of trivalent

antimony salts in humans is probably less than 10%. Gastrointestinal absorption of antimony is likely to be affected by numerous factors, including chemical form of the ingested antimony, particle size and solubility, 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.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of antimony in humans following dermal exposure.

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

2.3.2 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 2-4. The mean body burden of antimony is 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.

2.3.2.1 Inhalation Exposure

Information on the distribution of antimony in humans following inhalation exposure was not located. Blood is the main vehicle for the transport of absorbed antimony to various tissue compartments of the body. The relative partitioning between erythrocytes and plasma is a function of valency. Following exposure to trivalent antimony, erythrocyte levels are elevated, compared to the elevated plasma antimony levels after inhalation exposure to pentavalent antimony (Felicetti et al. 1974b). 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).

Valence-state differences also exist in the distribution of antimony to the rest of the body. In hamsters, 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). Outside of the respiratory tract, antimony accumulates in the liver, thyroid, skeleton, and fur; with the largest burden of antimony in the fur (Felicetti et al. 1974a, 1974b).

TABLE 2-4. Levels of Antimony Found in Various Tissues of Unexposed Humans

Tissue	Concentration (μg/g)	Reference
Hair	0.12	Muramatsu and Parr 1988
	0.096	Takagi et al. 1986
Adrenal gland	0.073	Sumino et al. 1975
Skin	0.096	Sumino et al. 1975
Lung	0.062	Sumino et al. 1975
Large intestine	0.047	Sumino et al. 1975
Trachea	0.045	Sumino et al. 1975
Cerebellum	0.030	Sumino et al. 1975
Kidney	0.043	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Small intestine	0.039	Sumino et al. 1975
Heart	0.032	Sumino et al. 1975
Pancreas	0.030	Sumino et al. 1975
Spleen	0.029	Sumino et al. 1975
Liver	0.023	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Ovary	0.021	Sumino et al. 1975
Testicle	0.017	Sumino et al. 1975
Cerebrum	0.016	Sumino et al. 1975
Blood	0.016	Sumino et al. 1975
	0.34	Mansour et al. 1967
Saliva	0.003	Olmez et al. 1978

2.3.2.2 Oral Exposure

Data on the distribution of antimony in humans following oral exposure to antimony were not located.

Following oral exposure in animals, the major sites of accumulation, outside of the gastrointestinal tract, are the liver, kidney, bone, lung, spleen, and thyroid. However, the rise in antimony levels in these tissues is not dose-related (Sunagawa 1981). This lack of dose-responsiveness may be a reflection of decreased absorption at higher antimony concentrations. Antimony levels tend to reach a plateau in the livers and lungs of voles fed a diet containing antimony trioxide (Ainsworth 1988).

Some species differences in animals exist in the elimination of antimony from the tissues. In rats, antimony is cleared slowly from the thyroid, with an elimination half-time of approximately 40 days (Gross et al. 1955); however, more than 50% of liver, lung, and kidney antimony is removed after 15 days following exposure in voles (Ainsworth 1988).

Evidence is insufficient to determine if there are valency differences in the distribution of orally administered antimony. Based on the inhalation data and the fact that higher liver concentrations were found in rats fed metallic antimony than those fed antimony trioxide (Sunagawa 1981), it is assumed that there are differences.

Pregnancy results in a higher antimony body burden in mice. However, transplacental transport of antimony appears limited. Exposure to antimony during lactation results in high antimony levels in newborns (Gerber et al. 1982).

2.3.2.3 Dermal Exposure

No information on the distribution of antimony in humans or animals following dermal exposure to antimony was located. However, judging from studies of the distribution of antimony following inhalation, oral, and parenteral exposure in animals, the major sites of accumulation are likely to include the liver, kidney, skeleton, spleen, and fur.

2.3.2.4 Other Routes of Exposure

No information on the distribution of antimony in humans following parenteral exposure was located. In animals, antimony is recovered primarily in the liver, with smaller amounts in the spleen, heart, lungs, and muscle (Gellhorn et al. 1946; Gerber et al. 1982).

Two hours after intraperitoneal injection of trivalent antimony, 95% of the antimony in the blood is incorporated into the erythrocytes, mainly in the hemoglobin fraction (Edel et al. 1983; Lippincott et al. 1947). Pentavalent

antimony is primarily distributed into the plasma fraction of blood (Edel et al. 1983).

Following intraperitoneal administration of trivalent antimony, a larger percentage of the administered dose is recovered in the liver than in the spleen. However, a smaller difference in antimony levels between the liver and spleen was observed when pentavalent antimony was administered (Gellhorn and van Dyke 1946).

2.3.3 Metabolism

Antimony is a metal and, therefore, does not undergo catabolism. 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. No information was located on the in vivo interconversion of trivalent and pentavalent antimony.

2.3.4 Excretion

2.3.4.1 Inhalation 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, 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. Based on studies in which antimony was parenterally administered to animals, the urine/feces ratio of antimony depends on valence state. Antimony is excreted predominantly in the urine following pentavalent antimony injection and in the feces after trivalent antimony administration (Edel et al. 1983; Felicetti et al. 1974b).

In animals, whole-body clearance of trivalent antimony tartrate occurs in two phases. Ninety percent of the initial body burden of antimony tartrate was excreted within the first 24 hours. The half-life of the slow phase was 16 days (Felicetti et al. 1974b).

2.3.4.2 Oral Exposure

Information on the excretion of antimony in humans following oral exposure was not located. However, 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. Animal studies have shown that ingested antimony is only partially absorbed from the gastrointestinal tract (Felicetti et al. 1974b; Gerber et al. 1982). Assuming that this is also true for humans, fecal excretion is probably an important route of excretion of ingested antimony 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 injected parenterally into humans or animals is excreted predominantly in the urine, whereas injected trivalent antimony is excreted in the feces (Edel et al. 1983; Goodwin and Page 1943; Rees et al. 1980).

2.3.4.3 Dermal Exposure

No information on the excretion of antimony following dermal exposure in humans or animals was located. However, 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 dermal exposure in humans. Antimony that is absorbed through the skin will be excreted in urine and feces to a variable degree, depending on the chemical species. Pentavalent antimony injected parenterally into humans or animals is excreted predominantly in urine, whereas injected trivalent antimony is excreted in feces (Edel et al. 1983; Goodwin and Page 1943; Rees et al. 1980).

2.3.4.4 Other Routes of Exposure

Pentavalent antimony is rapidly excreted in humans following intravenous or intramuscular administration, with greater than 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).

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. 1983j.

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).

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; the slower phase was 76 hours (Chulay et al. 1988).

2. HEALTH EFFECTS

2.4 RELEVANCE TO PUBLIC HEALTH

Adverse health effects have been observed in humans and animals following exposure to antimony and antimony compounds. Metallic antimony, organic forms, and inorganic forms of antimony were included in this profile. The organic forms of antimony discussed are potassium antimony tartrate, sodium antimony tartrate, and antimony acetate. Also included are the antimony-containing drugs stibocaptate (sodium antimony-2,3-meso-di-mercapto succinate) also referred to as astiban, and stibophen (bis[4,5-dihydroxy- 1,3-benzenedisulfonato(4)-O^4, O^5]-antimonate (5-) pentasodium heptahydrate) also called fuadin. Trivalent inorganic antimony compounds (antimony trioxide, antimony trichloride, antimony trisulfide), pentavalent inorganic compounds (antimony pentoxide, antimony pentachloride, and antimony pentasulfide), and stibine are also discussed. The toxicity data for antimony and compounds have been summarized across compounds; if differences in the toxicity between the various antimony compounds are known, this information will be presented in a compound specific discussion.

The toxicological effects of antimony in humans following inhalation or oral exposure are pneumoconiosis, altered EKG readings, increased blood pressure, abdominal distress, ulcers, dermatosis, and ocular irritation. No effects were found in humans after dermal exposure to antimony. There are several beneficial uses of antimony. Antimony and its compounds are among the oldest known remedies in the practice of medicine. Currently, antimony compounds are used to treat two parasitic diseases, schistosomiasis and leishmaniasis. Toxic side effects in humans following intraperitoneal, intravenous, or intramuscular injection of an antimony-containing drug have been reported. These effects include altered EKG, anemia, vomiting, diarrhea, joint and/or muscle pain, and death.

Similar toxicological effects have been reported in animals following inhalation, oral, or dermal exposure to antimony. These effects include fibrosis in the lung, altered EKG readings, myocardial damage, vomiting and diarrhea in dogs, parenchymatous degeneration in the liver and kidney, muscle weakness, difficulty in moving, developmental effects, and lung cancer. In addition, degeneration of the myoneural junction has been observed in animals following parenteral administration of antimony.

Inhalation and oral MRLs for antimony and compounds were not derived. Damage to the lungs and myocardium has been observed in several species of animals following acute, intermediate, and chronic inhalation exposure (Brieger et al. 1954; Bio/dynamics 1985, 1990; Gross et al. 1952; Groth et al. 1986; Watt 1983). These effects have also been observed in humans chronically exposed to airborne antimony (Brieger et al. 1954; Potkonjak and Pavlovich 1983). At the lowest exposure levels tested, the adversity of the effects was considered to be serious. Thus, the data were inadequate for the derivation of an acute-, intermediate-, and chronic-duration inhalation MKL values.

2. HEALTH EFFECTS

The lowest LGAEL for acute oral exposure is from-a human report (Dunn 1928). Gastrointestinal disturbances were reported in workers who drank lemonade contaminated with potassium antimony tartrate. If the dose was administered throughout the day rather than consumed as a bolus administration, it is likely that the gastrointestinal disturbances would not be observed. Thus, this study would not be an appropriate basis for an acuteduration oral MRL. The intermediate-duration inhalation data suggest that the myocardium is a target of antimony toxicity. The intermediate oral studies did not examine sensitive end points (e.g., EKG) of myocardial damage. This deficiency precludes derivation of an intermediate duration oral MRL. Two chronic oral studies were identified (Schroeder et al. 1968, 1970). At the lowest dose tested, decreased lifespan was observed in rats; this is not an appropriate basis for a chronic-duration oral MRL.

Acute-, intermediate-, and chronic-duration dermal MRLs were not derived for antimony due to the lack of an appropriate methodology for the development of dermal MRLs.

Death. Death has not been reported in humans following inhalation, oral, or dermal exposure to antimony. However, acute exposure to approximately 2 mg antimony/kg/day as stibocaptate (a drug used to treat parasitic disease) administered intramuscularly resulted in the death of an adult and a child (Rugemalila 1980). Therefore, antimony may be lethal at sufficiently high exposure levels. Animal studies have provided some information about the relative lethality of various forms of antimony. Based on data from studies on parenterally administered antimony, relative lethality can be ranked as follows: antimony tartrate > metallic antimony > inorganic trivalent antimony (Bradley and Frederick 1941).

Systemic Effects

Respiratory Effects. The respiratory tract is a target in humans following inhalation exposure to antimony. Pneumoconiosis, impaired pulmonary function (airway obstruction, bronchospasm, and hyperinflation) and respiratory irritation (coughing and wheezing) have been observed in factory workers exposed to antimony dust (Cooper et al. 1968; Potkonjak and Pavlovich 1983). A relationship between exposure level and effect cannot be established from this data because the workers were also exposed to other compounds, including arsenic oxide, iron oxide, hydrogen chloride, and hydrogen sulfide.

Information on the health effects in animals following inhalation exposure to antimony supports the finding in humans that the respiratory tract is a target. Most of the respiratory effects observed in animals are associated with the physiological response to dust accumulation in the respiratory tract. Because of the large amount of antimony that is deposited in the lung during chronic inhalation, the proliferation of macrophages observed in rats exposed to 0.07 mg antimony/m^3 or greater continues several

months after the exposure termination (Bio/dynamics 1990). This increase in the number of alveolar macrophages may contribute to the development of fibrosis. Fibrosis and lipoid pneumonia have been reported in rats chronically exposed to 1.6 mg antimony/m^3 or higher as antimony trioxide or to 17.48 mg antimony/m3 as antimony trisulfide (Bio/dynamics 1990; Gross et al. 1952; Groth et al. 1986; Watt et al. 1980,1983; Wong et al. 1979). Respiratory effects have not been reported in humans or animals following oral or dermal exposure to antimony.

Although serious antimony-related lung disease has not been observed in humans, antimony-induced pneumoconiosis is associated with serious lung pathology in animals. Therefore, it is likely that, with sufficiently high or prolonged exposures, serious lung disease would occur in humans. In addition, the toxicity of inhaled antimony compounds may be greater for smaller particle sizes.

Cardiovascular Effects. The heart is another target organ in humans. Alterations in EKG readings and increased blood pressure have been reported in workers exposed to airborne antimony trisulfide (Brieger et al. 1954). In addition, altered EKG readings have been reported in individuals exposed to repeated injections of antimony (Dancaster et al. 1966; Honey 1960; Pandey et al. 1988). The antimony injections were part of a therapeutic treatment for parasitic disease. In some of these individuals, the EKG did not return to normal until 6 weeks after the last dose (Dancaster et al. 1966). Pentavalent antimony appears to be less cardiotoxic than the trivalent form. Altered EKG readings were observed after 4 days of trivalent antimony treatment (0.98 mg antimony/kg/day) (Dancaster et al. 1966); however, a change in EKG readings was not observed until after 3 weeks of pentavalent antimony injections (7.2 mg antimony/kg/day) (Pandey et al. 1988).

Altered EKG readings have also been observed in animals. In addition, decreased blood pressure, increased heart rate, and decreased contractile force have been observed following injection of trivalent antimony (Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966). The decreased blood pressure contrasts with the increased blood pressure observed in humans (Brieger et al. 1954). Studies on isolated dog hearts suggest that antimony exerts its effect on the myocardium directly, and that the effect persists after exposure is terminated (Bromberger-Barnea and Stephens 1965).

Gastrointestinal Effects. Historically, antimony has been known for its emetic properties. Vomiting, diarrhea, gastric discomfort, and ulcers have been reported in humans following inhalation or oral exposure to antimony. Amounts as low as 0.529 mg antimony/kg have resulted in vomiting. The gastrointestinal effects following inhalation exposure may have resulted from antimony being swallowed. Gastrointestinal effects have also been observed in humans receiving intramuscular injections of antimony (Harris 1956; Zaki et al. 1964). Similar gastrointestinal effects have been reported in animals following oral exposure to antimony.

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Hematological Effects. Hematological effects in humans following inhalation, oral, or dermal exposure to antimony have not been reported. However, hematological parameters were not measured in the human studies. Hemolytic anemia was reported in one subject following repeated injections of fuadin (stibophen) (Harris 1956). Fuadin is an antimony-containing compound used in the treatment of schistosomiasis. Alterations in hematological parameters have not been reported in animals exposed to antimony via inhalation or dermal routes. Decreased hemoglobin and hematocrit and altered erythrocyte count were observed in animals following oral exposure to metallic antimony or antimony trioxide (Smyth and Thompson 1945; Sunagawa 1981). The potential of antimony to cause hematological effects in humans is not known.

Musculoskeletal Effects. Musculoskeletal effects have not been reported in humans or animals following inhalation, oral, or dermal exposure to antimony. However, muscle and/or joint pain was reported in 30-50% of subjects injected with fuadin or astiban, which were administered as part of the therapeutic treatment of schistosomiasis. The joint pain was more severe in subjects receiving fuadin, although' the dose was four times less than the astiban dose (Zaki et al. 1964). This suggests differences in the toxicity of the different antimony compounds, which might explain why musculoskeletal effects have not been observed in humans by the other routes of exposure. Myoneural junction swelling was observed in mice following injection with potassium antimony tartrate (Mansour and Reese 1965). A more complete description of the myopathy observed in these mice is given in the neurological section. Because of the limited human and animal data, it is difficult to determine the significance of this effect to human health.

Hepatic Effects. Hepatic effects have not been observed in humans exposed to antimony. Parenchymatous degeneration in the liver was observed in rats and guinea pigs exposed to airborne antimony trioxide for 30 weeks or to antimony trisulfide for 5 days (Brieger et al. 1954; Dernehl et al. 1945). However, liver effects have not been observed in more recent intermediate-chronic-duration inhalation studies (Bio/dynamics 1985, 1990; Groth et al. 1986; Watt 1983; Wong et al. 1979). Swelling of the hepatic cords has been observed in rats orally exposed to metallic antimony or antimony trioxide (Hiraoka 1986). Since hepatic effects have not been observed in humans and animal data are inconsistent, it is not known if liver damage will occur in humans exposed to antimony.

Renal Effects. Renal effects have not been reported in humans following inhalation, oral, or dermal exposure to antimony. Tubular dilation and degeneration of the tubular epithelium have been observed in rats, rabbits, and guinea pigs acutely exposed to airborne antimony trisulfide or stibine gas (Brieger et al. 1954; Price et al. 1979). Kidney effects have not been reported in animals exposed to airborne antimony for an intermediate or chronic duration (Bio/dynamics 1985, 1990; Groth et al. 1986; Watt 1983; Wong et al. 1979). The kidneys were not examined in the oral and dermal exposure studies. The relevance of this effect to human health is not known.

2. HEALTH EFFECTS

Dermal/Ocular Effects. Dermatosis and ocular irritation have been reported in humans following exposure to airborne antimony and antimony via injection (Potkonjak and Vishnijich 1983; R&es 1953; Stevenson 1965; Zaki et al. 1964). The dermatitis associated with exposure to airborne antimony 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). Dermal and ocular exposure to antimony has resulted in minimal skin and eye irritation in animals and the formation of cataracts (Bio/dynamics 1985, 1990).

Other Systemic Effects. Hyperplasia of the reticuloendothelial cells in the peribronchiolar lymph nodes was observed in rats chronically exposed to airborne antimony (Bio/dynamics 1990). This effect is probably the result of the clearance of antimony particles from the lungs, and thus it is an effect that is likely to occur in humans.

Immunological Effects. Immunological effects have not been studied in humans or animals following inhalation, oral, dermal, or parenteral exposure to antimony.

Neurological Effects. Neurological effects have not been observed in humans following inhalation, oral, dermal, or parenteral exposure to antimony. Muscle weakness, difficulty in moving, and abnormal gait have been observed in animals follotring oral and dermal exposure to antimony trioxide (Fleming 1982; Myers et al. 1978). Decreased motor efficiency and dystonic torsion of the limbs were observed in mice receiving intraperitoneal injections of potassium antimony tartrate (Mansour and Reese 1965). Degenerative changes in the anterior horn cells of the lumbar cord, edema with hydropic degeneration in the sciatic nerve, and swelling of the myoneural junction were also observed in this mouse study. Because neurological effects have been observed in three species of animals (dogs, rats, and mice), these effects may also occur in humans exposed to high levels of antimony.

Developmental Effects. An increase in the number of spontaneous abortions was observed in women exposed to airborne antimony in the workplace. The exposure level was not reported in this study. No overt developmental effects were observed in the children of these women (Belyaeva 1967). No gross abnormalities were observed in the offspring of rats exposed to low levels of antimony trichloride in the drinking water (Rossi et al. 1987). The likelihood of antimony-induced developmental effects occurring in humans is not known.

Reproductive Effects. Human exposure to antimony dust in the workplace has resulted in disturbances in menstruation (Belyaeva 1967). In animals, the failure to conceive and metaplasia in the uterus have been observed following inhalation exposure to antimony trioxide (Belyaeva 1967). No information on the potential of antimony to cause reproductive effects in animals following

oral or dermal exposure was located. These data suggest a potential for antimony to cause reproductive effects in humans.

Genotoxic Effects. No in vivo genotoxicity studies were located. The results of in vitro genotoxicity studies are presented in Table 2-5. Positive results for chromosome breakage in human leukocytes were found (Paton and Allison 1972). Positive results were also found for DNA damage, viral transformation, and chromosomal aberrations. Gene mutation and transformation tests were negative. Because of the limited in vitro genotoxicity data and the lack of in vivo tests, the genotoxicity of antimony in humans cannot be determined.

Cancer. No information on the carcinogenic potential of antimony in humans was located. Inhalation exposure to antimony trioxide or antimony trisulfide produced lung tumors in rats (Groth et al. 1986; Watt 1980, 1983; Wong et al. 1979). Lung tumors were not observed in the Bio/dynamics (1990) study. The Watt (1980, 1983) and Bio/dynamics (1990) studies used similar concentrations of antimony trioxide. However, lung cancer was observed only in the Watt (1980, 1983) study. A possible explanation for the conflicting results is differences in the amount of antimony that was deposited in the lungs. Bio/dynamics (1990) asked the pathologist who examined the histopathology slides from the Watt (1980, 1983) study to also examine the slides from the Bio/dynamics (1990) study. The pathologist determined that the degree of pigmentation in the lungs (indicative of the amount of antimony in the lungs) was greater in the lungs of rats from the Watt (1980, 1983) study compared to those from the Bio/dynamics study (1990). However, why there were differences in antimony deposition and/or clearance between the studies is not known. The deposition and clearance of antimony depends on particle size (Felicetti et al. 1979b; Thomas et al. 1973). The smaller particles are deposited in the lower respiratory tract and are slowly cleared from the lung. The larger particles are deposited in the upper airways and are cleared more efficiently from the lung. Thus, antimony with smaller particle sizes come into contact with the lung tissue for a longer period of time; this may influence the carcinogenic potential. Because of differences in the methods used to assess particle size distribution between these two studies, a comparison of particle size distribution between the studies can not be made. The carcinogenicity of inhaled antimony also may vary with the chemical form of antimony, which will affect the solubility of antimony and, thereby, lung retention. The carcinogenicity of inhaled antimony is probably related to its deposition in the respiratory tract and the resulting reactive processes induced by its presence in the lung tissue. These include macrophage infiltration and fibrosis, typical of pneumoconiosis. The lung carcinogenicity of inhaled antimony may not, therefore, predict carcinogenic potential for other routes of exposure. Antimony has not produced cancer in rats or mice exposed by the oral route (Kanisawa and Schroeder 1969; Schroeder et al. 1968, 1970). There may be physiological differences in the deposition and clearance of antimony from the lungs between humans and rats. Thus, it is

TABLE 2-5. Genotoxicity of Antimony *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Form
Prokaryotic organisms:					
Bacillus subtilis	DNA damage	No data	+	Kanematsu et al. 1980	Trioxide; trichloride; pentachloride
Mammalian cells:					
Syrian hamster embryo cells	Viral transformation	No data	+	Casto et al. 1979	Acetate
Chinese hamster ovary cells	Gene mutation	-	-	Tu and Sivak 1984	Thioantimonate
	Chromosomal aberrations	+	+	Tu and Sivak 1984	Thioantimonate
BALB/c-3T3	Transformation	No data	-	Tu and Sivak 1984	Thioantimonate
Human leukocytes	Chromosome breakage	No data	+	Paton and Allison 1972	Sodium tartrate

+ = positive
- = negative

difficult to assess carcinogenic potential of antimony in humans. No information of carcinogenic potential of antimony following dermal application of antimony was located.

2.5 BIOMABKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to antimony are discussed in Section 2.5.1.

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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by antimony are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2. HEALTH EFFECTS

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Antimony

Elevated blood, hair, urine, and fecal levels of antimony indicate high exposure to antimony. A significant correlation exists 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 antimony/kg/day). Factory workers exposed to antimony trioxide (0.042-0.70 mg antimony/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. Animal data suggest that urine and blood levels remain elevated several days after exposure (Felicetti et al. 1974b).

No effect biomarkers that could be used to implicate exposure to antimony were found.

2.5.2 Biomarkers Used to Characterize Effects Caused by Antimony

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.

2.6 INTERACTIONS WITH OTHER CHEMICALS

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

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Individuals with existing chronic respiratory or cardiovascular disease or problems would probably be at special risk, since antimony probably exacerbates one or both types of health problems. Because antimony is excreted in the urine, individuals with kidney dysfunction may be unusually susceptible.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to antimony. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to antimony. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

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Adverse health effects in humans following antimony exposure appear to target on the respiratory and cardiovascular systems. Eye and skin irritation have also been noted.

Human exposure to antimony may occur by inhalation, ingestion, or by dermal contact. Mitigation approaches to reduce absorption of antimony have included general recommendations of separating contaminated food, water, air, and clothing from the exposed individual. Externally, exposed eyes and skin are flushed with a clean neutral solution such as water or normal saline. Administration of water or milk and a cathartic such as magnesium sulfate has been recommended by Stutz and Janusz (1988) for treatment following oral exposure to antimony. This would reduce the concentration of antimony in the stomach, but is not likely to affect its intestinal absorption. Administration of activated charcoal following exposure to organic compounds is thought to be effective in preventing absorption (Stutz and Janusz 1988).

Antimony may be found in the blood and urine several days after exposure. It also can be found in the hair (Dorea et al. 1989). Pentavalent antimony is rapidly excreted in humans following intravenous or intramuscular administration, with greater than 50% excreted in the urine 6 hours after injection (Goodwin and Page 1943; Rees et al. 1980). Trivalent antimony is not as rapidly excreted in the urine and is primarily excreted in the feces over a 24 hour period of time as noted after intraperitoneal administration in laboratory animals (Edel et al. 1983).

Chelation therapy with British anti-Lewisite (BAL) may be the most effective mitigation approach following absorption of trivalent antimony compounds into the blood stream (Ellenhorn and Barceloux 1988; Haddad and Inchester 1990). Antimony can covalently bind with sulfhydryl groups. BAL, a dithiol compound with two vicinal sulfur atoms, competes with the critical binding sites that may possibly be responsible for the toxic effects. There is no evidence that BAL is useful following stibine gas exposure (Ellenhorn and Barceloux 1988).

Dialysis may be the most effective method for mitigation of pentavalent antimony. Pentavalent antimony in the blood resides mainly in the plasma in an easily dialyzable form (Edel et al. 1983); Dialysis treatment following exposure to trivalent antimony may not be as effective. The majority of trivalent antimony found in blood is incorporated into the red blood cell fraction in a hard dialyzable form (Edel et al. 1983).

2.9 ADEQUACY OF THE DATABASE

Section 104(i)(S) 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 the National Toxicology Program (NTP),

is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of antimony.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

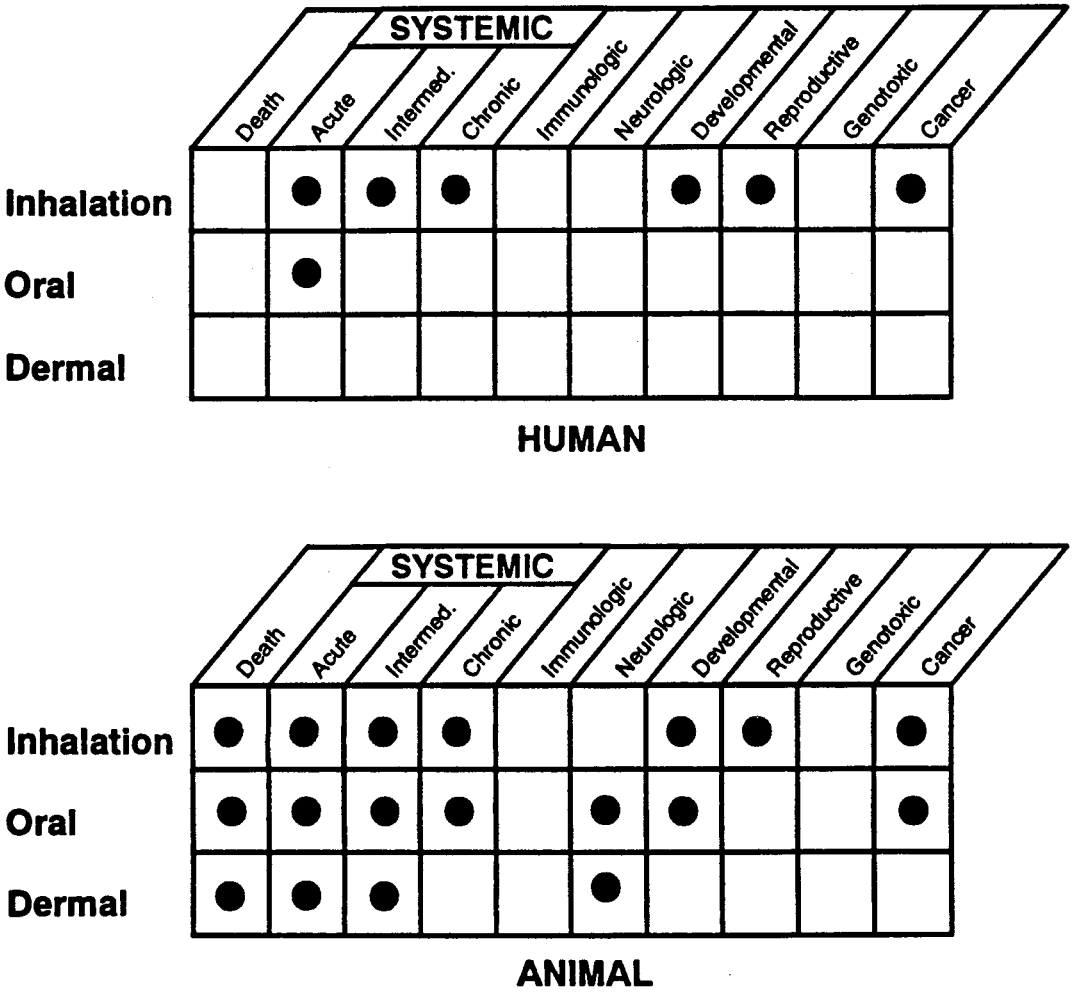
2.9.1 Existing Information on Health Effects of Antimony

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to antimony are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of antimony. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

As seen in Figure 2-3, information on the health effects of antimony in humans following inhalation, oral, or dermal exposure is limited. 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. The dermal data on humans is limited to a study in which antimony was applied to the skin of volunteers.

As compared to the human data, more complete information on the systemic health effects of antimony in animals was located. Although there are several reliable intermediate and chronic duration studies that examined numerous toxicological end points following exposure to airborne inorganic trivalent antimony (primarily antimony trioxide), most of the studies utilized rats. One inhalation reproductive/developmental study was located. 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 located. The acute and intermediate toxicity of dermally applied antimony trioxide, antimony oxide, and antimony thioantimonate has been examined. However, these studies did not examine the systemic toxicity of antimony; they were designed to assess the dermal and/or ocular toxicity of antimony.

FIGURE 2-3. Existing Information on Health Effects of Antimony



● Existing Studies

2.9.2 Data Needs

Acute-Duration Exposure. Information on the target organs of acute exposure in humans to antimony is limited. Based on one human study, the gastrointestinal tract appears to be a target following inhalation exposure to antimony (Taylor 1966). Animal studies have shown that the respiratory tract and cardiovascular, hepatic, and renal effects occur after exposure to airborne antimony (Brieger et al. 1954; Price et al. 1979). The respiratory and cardiovascular effects occur at a lower exposure levels than those associated with gastrointestinal effects in humans. An acute inhalation MRL could not be derived from this animal data because serious myocardial effects were observed at the lowest exposure level tested. The gastrointestinal tract also appears to be a target in humans following oral exposure to antimony. This is based on a report of workers who accidentally drank lemonade contaminated with potassium antimony tartrate (Dunn 1928). An acute oral MRL could not be derived from this study. Acute animal data also suggest that the gastrointestinal tract is a target system (Fleming 1982; Houpt et al. 1984; Myers et al. 1978). However, two of the three acute animal studies did not perform complete histological examinations, thus there may be other target organs that have not been identified (Fleming 1982; Houpt et al. 1984; Myers et al. 1978). There is no information on the target organs in humans following dermal exposure to antimony. Application of antimony to the skin or eyes of animals results in mild irritation (Gross et al. 1955; Horton et al. 1986; Myers et al. 1978; Wil Research Lab 1979). A majority of the animal studies only examined the skin or eyes following dermal/ocular exposure to antimony. Toxicokinetic data that might allow route-to-route extrapolations of health effects were not found. Knowledge about the acute toxicity of antimony is important because people living near hazardous waste sites might be exposed to antimony for brief periods. Information about the toxicity of different antimony compounds, as well as differences in valence states, was not located. Additional acute-duration studies by the inhalation, oral, and dermal routes would provide information on differences in the potency of various antimony compounds, as well as on the thresholds for systemic toxicity due to acute-duration exposure to antimony.

Intermediate-Duration Exposure. Human target organs/systems following exposure to airborne antimony include the respiratory tract and gastrointestinal tract and skin (Brieger et al. 1954; Renes 1953; Stevenson 1965). No reports of health effects in humans following oral or dermal exposure were located. Animal data suggest that the heart and respiratory tract may be targets following inhalation exposure (Brieger et al. 1954; Bio/dynamics 1985). Developmental and reproductive effects have also been reported in animals (Belyaeva 1967). There is no information on human health effects following oral exposure to antimony. Oral exposure of animals to antimony has resulted in adverse health effects on the liver, cardiovascular system, gastrointestinal tract, and mild hematological effects (Angrisani 1988; Fleming 1982; Hiraoka 1986; Marmo et al. 1987; Rossi et al. 1987; Smyth

and Thompson 1945; Sunagawa 1981). No reports of human health effects following dermal exposure were located. No adverse health effects were observed in animals following intermediate duration dermal exposure (Horton et al. 1986). EKG readings are a sensitive indicator of myocardial damage; however, in the oral and dermal intermediate-duration studies this end point was not examined. Because the exposure levels tested were higher than the threshold levels for respiratory tract effects, and/or because EKG readings were not taken, inhalation and oral MKLs could not be derived. Toxicokinetic data that might allow extrapolation of health effects across routes of administration were not located. Information on the relative toxicity of the different antimony compounds has not been assessed. Intermediate-duration studies by inhalation, oral, and dermal routes would provide information on the thresholds for systemic toxicity, as well as on the differences in the potency of various antimony compounds. This information could be relevant to human exposure because people living near hazardous waste sites may be exposed to a variety of antimony compounds for an intermediate-duration.

Chronic-Duration Exposure and Cancer. There are several human and animal chronic inhalation studies that indicate the targets appear to be the respiratory tract, heart, eye, and skin (Brieger et al. 1954; Cooper et al 1968; Potkonjak and Pavlovich 1983). However, functional changes in the cardiovascular system were not assessed in the animal inhalation studies (Bio/dynamic 1990; Gross et al. 1952; Groth et al. 1986; Watt 1980, 1983; Wong et al. 1979). A no-effect level (NOEL) for respiratory or cardiovascular effects following exposure to antimony was not identified in the available literature. The NOEL is an important level in evaluating the risk of exposure to antimony, and it can be used along with protective uncertainty factors to help determine the amount of antimony humans can be exposed to without experiencing health effects. The chronic inhalation studies in animals examined only the toxicologic effects in rats; thus, interspecies differences could not be assessed. No target organs were identified in humans or animals following oral exposure to antimony (Kanisawa and Schroeder 1989; Schroeder et al. 1968, 1970). In addition, the data from the oral and inhalation studies were insufficient for deriving a chronic MEL. There is no information on the health effects in humans and animals following dermal exposure. Well-designed oral experiments, using several exposure levels and measuring all sensitive toxicological end points, would provide information on the health effects associated with long-term exposure to antimony. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to antimony for many years.

No studies were located regarding the carcinogenicity of antimony in humans following inhalation, oral, or dermal exposure. Evidence for the carcinogenicity of inhaled antimony in animals is mixed. Two studies reported lung tumors in rats exposed to relatively low levels of antimony trioxide (Groth et al. 1986; Watt 1983; Wong et al. 1979). A study using a similar exposure level did not find evidence of carcinogenicity (Bio/dynamics 1990).

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Differences in the amount of antimony deposited and/or cleared from the lungs were reported. It is not known if the conflicting results were due to differences in particle sizes. A study comparing the effects of different particle sizes would determine if the particle size of the inhaled antimony determines the carcinogenic potential of antimony. The increased incidence of lung tumors appears to be route specific. There is no evidence of increased incidence of cancer in humans as a result of oral exposure to antimony. The oral cancer data in animals are limited to studies that used very low levels of antimony (Kanisawa and Schroeder 1989; Schroeder et al. 1968, 1970). Oral studies have shown that antimony tends to accumulate in the liver and gastrointestinal tract (Ainsworth 1988; Sunagawa 1981); it is not known if this results in cancer. No dermal cancer studies in humans or animals was located. Oral and dermal studies in rodents using several exposure levels including the maximum tolerated level would provide useful information because prolonged exposure to antimony in humans may occur.

Genotoxicity. There are no in vivo genotoxicity studies in humans or animals. In vitro studies using human leukocytes were positive for chromosome breakage (Paton and Allison 1972). Results were mixed in in vitro studies using mammalian cells (Casto et al. 1979; Tu and Sivak 1984), and positive for DNA damage in Bacillus subtilis (Kanematsu et al. 1980). Additional in vitro and in vivo genotoxicity studies would enable better estimation of the actual genotoxic threat posed by antimony to people exposed in the environment.

Reproductive Toxicity. Women exposed to antimony in the workplace have reported menstrual disturbances and a higher incidence of spontaneous abortions as compared to 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 (Belaeva 1967). In addition, studies on the distribution of antimony following oral administration in animals have shown high levels of antimony in the testes (Sunagawa 1981). It is not known whether these high levels of antimony could result in functional changes. There are no data on reproductive effects following oral or dermal exposure to humans and animals. There are insufficient toxicokinetic data to make route-to-route extrapolation. A well-designed study to assess the effects of orally or dermally administered antimony on reproductive performance would provide information on possible reproductive effects that might be relevant to humans.

Developmental Toxicity. 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. Developmental effects were not observed in the offspring of rats exposed orally to antimony trichloride

(Rossi et al. 1987). An animal study has shown that antimony is not efficiently transported across the placenta (Gerber et al. 1982). However, there is evidence of high levels of antimony in unexposed newborn nursed by exposed female mice (Gerber et al. 1982). A study in which animals are exposed throughout gestation and lactation would provide information on the potential of antimony to result in developmental effects in humans.

Immunotoxicity. Immunotoxicity following inhalation, oral, or dermal exposure have not been studied in humans or animals. Immunological end points should be examined in the intermediate or chronic studies, especially since antimony has been shown to accumulate in the spleen (Sunagawa 1981).

Neurotoxicity. Neurotoxic effects have not been observed in humans following inhalation, intramuscular, and intraperitoneal exposure to antimony. Neuromuscular effects have been observed in animals following oral, dermal, and intraperitoneal administration (Fleming 1982; Mansour and Reese 1965; Myers et al. 1978). Furthermore, myopathy has been observed in mice exposed via intraperitoneal injection (Mansour and Reese 1965). Although this effect has not been observed by other routes of exposure there is no reason to suspect that it would not occur. Sensitive tests of neurophysiological function may detect early sign of neurotoxicity following inhalation, oral, or dermal exposure to antimony.

Epidemiological and Human Dosimetry Studies. There are several epidemiological occupational exposure studies (Brieger et al. 1954; Cooper et al. 1968; Potkonjak and Pavlovich 1983; RBnes 1953; Stevenson 1965). However, most of these studies are incomplete because the exposure level and/or particle size of the airborne antimony was not reported and/or the workers were often exposed to a variety of other compounds. In addition, cardiovascular toxicity, a sensitive end point of antimony toxicity, was not always assessed. No epidemiological or human dosimetry studies in which individuals were exposed to antimony orally or dermally were located. Epidemiological studies would be useful in order to determine the effects of long-term exposure on humans, with particular attention paid to cardiovascular and respiratory effects. If a cause/effect relationship was established between antimony exposure and health effects in humans, monitoring of individuals living near hazardous waste sites could be performed in order to verify that exposure levels do not exceed recommended limits and that body tissue and fluid levels remain below potentially hazardous levels.

Biomarkers of Exposure and Effect. Because antimony is not catabolized in the body, metabolites could not be used as a biomarker. Thus, the only biomarker of exposure would be measurement of antimony itself. Antimony levels are increased in the blood, urine, and feces following exposure to antimony (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). However, because antimony is poorly absorbed from the lung,

measurement of antimony levels in body fluids may not reflect the exposure level of airborne antimony (Felicetti et al. 1974a, 1974b; Thomas et al. 1973). The relationship between exposure level and concentration of antimony in various body fluids has not been established. Development of a biomarker with more exposure/dose data would aid in future medical surveillance that could lead to better detection of exposure.

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 (Ainsworth 1988; Cooper et al. 1968; Edel et al. 1983; Felicetti et al. 1974a, 1974b; Gerber et al. 1982; Gerhardsson et al. 1982; Goodwin and Page 1943; Ludersdorf et al. 1987; Rees et al. 1980; Sumino et al. 1975; Sunagawa 1981; Thomas et al. 1973). 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 has 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, or 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. A study that examined these aspects of antimony would be useful in assessing the potential target organs following dermal exposure to antimony.

Comparative Toxicokinetics. Species differences in the toxicokinetics of antimony have been identified (Ainsworth 1988; 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 decide which animal species is the best model for assessing the toxicity of antimony. Information on the behavior of antimony in humans would be useful.

Mitigation of Effects. Chelation therapy with BAL has been shown to effectively mitigate the toxicity of trivalent antimony compounds in humans (Ellenhorn and Barceloux 1988; Haddad and Winchester 1990). Although BAL has been found to form stable chelates in vivo with antimony, it is not known if there are adverse side effects associated with the treatment. Studies examining the effectiveness of chelating agents and possible side effects would be helpful in determining the most effective treatment for antimony toxicity. Antimony is widely distributed throughout the body. The hair and

skin contain the highest levels of antimony. The adrenal glands, lung, large intestine, trachea, cerebellum, and kidneys also contain relatively high levels of antimony (Muramatsu and Parr 1988; Sumino et al. 1975). No information on methods of mitigating body stores were located. Studies that examined such methods would be useful in the treatment of antimony toxicity.

2.9.3 On-going Studies

NTP (1990) has recently completed a 14-day drinking water study in which groups of male and female Fischer 344 rats and B6C3Fl mice were given drinking water containing potassium antimony tartrate. The doses in rats were 0, 16, 28, 59, 94, and 168 mg/kg/day; for mice, they were 0, 59, 98, 174, 273, and 407 mg/kg/day. In rats, the only effects observed were an increase in relative liver and kidney (females only) weights in the high dose group. Focal areas of ulceration with necrosis and inflammation of the squamous mucosa of the forestomach were observed in the high dose mice. A final report of this study is currently not available.

NTP (1990) has also completed a 13-week intraperitoneal injection study. In this study, inflammation and/or fibrosis of the liver were observed in mice dosed with 60 mg/kg potassium antimony tartrate every other day. Degeneration was evident in the kidneys of male rats dosed with 24 mg/kg every other day. A final report of this study is currently not available.

Genotoxicity tests were negative in Salmonella typhimurium strains TAl00, TA1535, TA97, or TA98 for antimony potassium tartrate with and without metabolic activation (NTP, 1990).

NIOSH is conducting an epidemiological study using a cohort of antimony smelter workers to determine the possible association between exposure to antimony and the risk of developing lung cancer (Federal Research in Progress 1989).