

## 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 sulfur trioxide/sulfuric acid. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

This profile does not discuss studies regarding exposure to sulfur dioxide, from which sulfur trioxide and sulfuric acid are formed. Studies regarding effects of sulfur dioxide are discussed in a separate ATSDR profile (ATSDR 1997).

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

### 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal; and then by health effect--death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (14 days or less), 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. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are

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used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOABLs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others 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 Bevels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User’s Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

### **2.2.1 Inhalation Exposure**

Few studies were identified regarding the toxic effects of sulfur trioxide. Within the respiratory tract, sulfur trioxide reacts rapidly with water to form sulfuric acid (IARC 1992). Therefore, the adverse effects of sulfur trioxide are expected to be the same as those of sulfuric acid.

There are many factors, in addition to exposure concentration, that determine the response to the inhalation of sulfuric acid aerosols. One factor is aerosol size which determines the location in the respiratory tract where sulfuric acid aerosols will deposit and result in effects. Humidity, both in the environment and in the respiratory tract, helps to determine the aerosol size.

Growth of sulfuric acid aerosols in response to humidity in airways results in greater respiratory deposition compared to deposition of inert particles (Carabine and Maddock 1976). Likelihood of pulmonary deposition is increased by depth of penetration and particle growth. Because small sulfuric acid particles grow upon contact with humidified airways, they will penetrate deeper into the lung than inert particles of the same size as the enlarged, humidified particles. Growth of acid particles also increases retention because they may

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initially enter small airways, but following expansion, may be too large for exhalation through the same airways. Therefore deposition will also be greater as compared to that of inert particles of the same size as the original acid particle prior to inhalation.

Inert aerosols, which do not change size as they enter the respiratory tract, deposit in the nasopharyngeal region by inertial impaction if they are 5-30  $\mu\text{m}$  in diameter; in the tracheobronchial region by sedimentation if they are 1-5  $\mu\text{m}$  in diameter; and in the alveolar region by diffusion if they are  $\leq 1$   $\mu\text{m}$  in diameter (Witschi and Last 1996).

Aerosols are usually a range of sizes that approximate a log-normal distribution. This size distribution is most frequently described by the median or geometric mean and the geometric standard deviation (Witschi and Last 1996). For studies of sulfuric acid aerosols, the diameters often reported are the mass median diameter (MMD) and the mass median aerodynamic diameter (MMAD) which takes into account both the density of the particle and the aerodynamic drag. Several inhalation studies of sulfuric acid aerosol report aerosol size as count median diameter (CMD) or volume median diameter (VMD). Aerosol size in  $\mu\text{m}$  is presented in the inhalation LSE table (Table 2-B), and the type of measurement is indicated. In Figure 2-1, aerosol sizes are indicated with footnotes as ultrafine (U)  $<0.1$   $\mu\text{m}$ , small (S) 0.1- $<1$   $\mu\text{m}$ , medium (M) 1- $<5$   $\mu\text{m}$ , and large (L) 5-30  $\mu\text{m}$ . Acid aerosols typically found in the ambient air have an MMAD of 0.3-0.6  $\mu\text{m}$ , while industrial aerosols can have MMADs as large as 14  $\mu\text{m}$  (Lippmann et al. 1987).

In addition to aerosol size, conditions of exposure are very important for determining the effect of sulfuric acid. For example, breathing rate, which is affected by physical activity, and the method of breathing (e.g., nose, mouth, or oronasal) help to determine where in the respiratory tract the aerosol deposits; the site of deposition determines the effect of the aerosol. How much of the acid is neutralized by ammonia or other alkaline substances, both in the ambient environment and within the respiratory tract, also determines the effects of sulfuric acid aerosols. Ammonia is emitted in breath and sweat, with concentrations of 120-1280 ppb measured in the exhaled air of humans (Suh et al. 1992). Therefore, as sulfuric acid enters the breathing zone it may be neutralized which results in lower personal exposure. More information about sources of ammonia can be found in the ATSDR profile on ammonia (ATSDR 1990).

The acid neutralization capacity of the respiratory mucus may also determine whether or not inhalation of sulfuric acid aerosols will result in a response. For example, it has been suggested that asthmatics are more sensitive to sulfuric acid because the pH of their mucus is lower than normal subjects (Holma 1985). In the

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discussions that follow, conditions of exposure, especially in human exposure studies, will be presented. Exposures were whole-body chamber exposures unless indicated otherwise. In addition, in the inhalation LSE table (Table 2-1), studies in which the volunteers were asthmatics are indicated as “human-a.” The non-asthmatic subjects are designated as “human-n.”

**2.2.1.1 Death**

Studies regarding death of humans following acute- and intermediate-duration inhalation exposure to sulfuric acid aerosols were not identified in recent years. Increased mortality, especially of elderly persons and those with preexisting cardiac and respiratory disease, has been reported during or shortly after air pollution episodes (Costa and Amdur 1996). Because it is not possible to clearly separate the effects of sulfuric acid aerosols from other pollutants, including particulates, sulfur dioxide, and ozone, these studies are not discussed. In general, increased mortality seems to correlate more closely with particulate matter, including sulfuric acid aerosols. In a study that tried to separate the effects of sulfuric acid aerosols from sulfur dioxide and from British smoke (a measure of particulates), the log of sulfuric acid aerosol concentrations in London was more strongly correlated with total mortality than either sulfur dioxide or British smoke (Thurston et al. 1989). The authors of the study concluded that their results were consistent with the hypothesis that sulfuric acid is the portion of the particulate mass with greatest health significance. No association between mortality and environmental sulfate concentrations was observed among 6,340 nonsmoking persons living in California (Abbey et al. 1995). Overall mortality of workers was not associated with acid exposure at steel factories (Beaumont et al. 1987) or at a sulfuric acid plant (Englander et al. 1988).

Numerous studies are available concerning the mortality of animals following inhalation exposure to sulfuric acid. One-hour  $LC_{50}$ s of 347 and 420 ppm fuming sulfuric acid have been reported for female and male rats, respectively (Vernot et al. 1977). Fuming sulfuric acid is sulfuric acid with up to 80% free sulfur trioxide (Budavari 1989). The percentage of sulfur trioxide in the Vernot et al. (1977) study was not stated. The  $LC_{50}$  values expressed as mg sulfur trioxide/  $m^3$  were 1,136 and 1,375 for female and male rats, respectively. Because fuming sulfuric acid was used in this study, the Vernot et al. (1977) study is not presented in Table 2- 1 or Figure 2- 1.

The lowest concentration of sulfuric acid aerosols that resulted in the death of rats was 383 mg/  $m^3$  (Treon et al. 1950). One rat died during the first day of a 7-hour exposure, and one rat died on the second day of a 7-hour exposure. Following one 7-hour exposure, 2 of 2 rats died at 699 mg/ $m^3$ , while all rats survived a 7-

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hour exposure to sulfuric acid aerosols at 461 mg/ m<sup>3</sup> (Treon et al. 1950). Following one 3.5-hour sulfuric acid aerosol exposure, 2 of 2 rats died at 1,470 mg/ m<sup>3</sup> with no deaths observed at 718 mg/ m<sup>3</sup> (Treon et al. 1950). The aerosol size used in the Treon et al. (1950) study was described as being in the range of 1-2 µm . In a 5-day exposure study in which the duration of the exposure each day was not stated, no rats died during exposure to 100 mg/ m<sup>3</sup> sulfuric acid aerosols at an MMAD of 0.72 µm (Cavender et al. 1977).

Mice were more susceptible to sulfuric acid aerosol exposure (diameter 1-2 µm) than rats (Treon et al. 1950). Following 5 daily 7-hour exposures, 4 of 5 mice died at 383 mg/ m<sup>3</sup>, with all surviving at 203 mg/ m<sup>3</sup>. Exposure for 7 hours resulted in the deaths of 2 of 5 mice at 699 mg/ m<sup>3</sup>, with all surviving at 461 mg/ m<sup>3</sup>, while exposure for 3.5 hours resulted in the deaths of 2 of 5 at 549 mg/ m<sup>3</sup>. Lower concentrations of sulfuric acid were not studied in mice exposed for 3.5 hours.

Among the species tested, guinea pigs are the most sensitive to exposure to sulfuric acid aerosols. During a 1-hour exposure to 52-61 mg/ m<sup>3</sup> sulfuric acid (MM/D 0.8-2.1 µm), about 6% of the exposed guinea pigs died (Stengel et al. 1993). The lowest concentration of the range is shown in Table 2-1 and Figure 2-1. The number of guinea pigs exposed was not stated. Before death, the guinea pigs developed labored breathing. Exposure of guinea pigs to 87 mg/ m<sup>3</sup> sulfuric acid aerosols in the range of 1-2 µm resulted in the death of all 3 exposed animals within 2.75 hours (Treon et al. 1950). The deaths of guinea pigs were attributed to an acute respiratory response to the acid exposure.

Younger guinea pigs are more sensitive to sulfuric acid aerosols than older guinea pigs. For guinea pigs exposed to sulfuric acid aerosols with a mean aerosol size of 1 µm, 8-hour LC<sub>50</sub>s of 18 and 50 mg/ m<sup>3</sup> were reported for 1-2-month-old and 1.5-year-old guinea pigs, respectively (Amdur et al. 1952a). During a 72-hour exposure to 12 mg/ m<sup>3</sup> sulfuric acid aerosols (mean particle size 1 µm), approximately 10% of the exposed guinea pigs died during the first 8 hours, with no additional deaths occurring (Amdur et al. 1952a). No guinea pigs exposed to 8 mg/ m<sup>3</sup> sulfuric acid aerosol for 72 hours died. The effects observed in the guinea pigs that died included gross areas of hemorrhage in the lungs, which were frequently most pronounced around the hilar regions, surface hemorrhage of the adrenal glands, and nasal bleeding at higher concentrations. Microscopically, hemorrhage and edema were observed in the lungs, with leukocytes and erythrocytes in the alveolar spaces. Congestion of the bronchi, alveoli, and blood vessels was also observed.

The effect of aerosol size on survival of guinea pigs exposed to sulfuric acid aerosols has been studied. Following exposure to sulfuric acid aerosols with MMADs of 0.8 and 0.4 µm, LC<sub>50</sub>s of 30.3 and

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>109 mg/ m<sup>3</sup>, respectively, were reported for guinea pigs exposed for 8 hours (Wolff et al. 1979). In another study, 8-hour LC<sub>50,s</sub> of 59.8 and 27.3 mg/ m<sup>3</sup> were reported for aerosols with MMADs of 0.8 and 2.7 μm, respectively (Pattle et al. 1956). Pattle et al. (1956) also showed that a lowered ambient temperature enhanced the toxicity of sulfuric acid aerosols in guinea pigs. For an aerosol of MMAD 0.8 μm, the LC<sub>50s</sub> were 59.8 and 46.9 mg/ m<sup>3</sup> at 20°C and 0°C respectively.

Following exposure of rabbits to sulfuric acid aerosols with a diameter in the range of 1-2 μm, 1 of 2 died following a 3.5-hour exposure to 1,470 mg/ m<sup>3</sup>, 1 of 2 died following a 7-hour exposure to 1,610 mg/ m<sup>3</sup>, and 2 of 2 died following five daily 7-hour exposures to 383 mg/ m<sup>3</sup> (Treon et al. 1950). No deaths of rabbits occurred at 718 mg/m<sup>3</sup> for 3.5 hours, 699 mg/m<sup>3</sup> for 7 hours, or 203 mg/ m<sup>3</sup> for 5 daily 7-hour exposures. Among the exposed rabbits that died, most of the deaths were attributed to infectious pneumonia that occurred after the chemical injury, rather than an acute respiratory response as observed in guinea pigs. From their results in rats, mice, guinea pigs, and rabbits, Treon et al. (1950) concluded that at relatively high concentrations of sulfuric acid aerosols, the duration of exposure was more important in determining lethality than exposure concentration.

No effect on survival was observed in cynomolgus monkeys or guinea pigs exposed to sulfuric acid aerosols 23.3 hours/day, 7 days/week, for 78 weeks (monkeys) or 52 weeks (guinea pigs) (Alarie et al. 1973). The monkeys were exposed at concentrations of 0,0.38,0.48,2.43, or 4.79 mg/ m<sup>3</sup> (MMDs of 2.15,0.54,3.6, and 0.73 μm, respectively), and the guinea pigs were exposed at concentrations of 0,0.08, or 0.1 mg/ m<sup>3</sup> (MMDs of 0.84 and 2.78 μm, respectively).

All LOAEL and LC<sub>50</sub> values from each reliable study for death in each species for acute exposure are recorded in Table 2- 1 and plotted in Figure 2- 1.

### 2.2.1.2 Systemic Effects

The highest NOAEL and representative LOAEL values from reliable studies for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-1.

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (NS)	3.5 hr (WB)				1470 (2/2 died)	Treon et al. 1950 diameter 1-2
2	Rat (NS)	7 hr (WB)				699 (2/2 died)	Treon et al. 1950 diameter 1-2
3	Rat (NS)	2 d 7 hr/d (WB)				383 (2/2 died)	Treon et al. 1950 diameter 1-2
4	Mouse (NS)	3.5 hr (WB)				549 (2/5 died)	Treon et al. 1950 diameter 1-2
5	Mouse (NS)	7 hr (WB)				699 (2/5 died)	Treon et al. 1950 diameter 1-2
6	Mouse (NS)	5 d 7 hr/d (WB)				383 (4/5 died)	Treon et al. 1950 diameter 1-2
7	Gn Pig (NS)	8 hr (WB)				18 (LC <sub>50</sub> 1-2 months old)  50 (LC <sub>50</sub> 1.5 years old)	Amdur et al. 1952a mean particle size 1

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
8	Gn Pig (NS)	72 hr (WB)				12 (approximately 10% died)	Amdur et al. 1952a mean particle size 1
9	Gn Pig (NS)	8 hr (WB)				27.3 (LC <sub>50</sub> )	Pattle et al. 1956 MMAD 2.7
10	Gn Pig (NS)	8 hr (WB)				59.8 (LC <sub>50</sub> at 20°C) 46.9 (LC <sub>50</sub> at 0°C)	Pattle et al. 1956 MMAD 0.8
11	Gn Pig (Hartley)	1 hr (N)				52 M (about 6% died, total number exposed not stated)	Stengel et al. 1993 MMAD 0.8-2.1
12	Gn Pig (NS)	2.75 hr (WB)				87 (3/3 died)	Treon et al. 1950 diameter 1-2
13	Gn Pig (Hartley)	8 hr (WB)				30.3 (LC <sub>50</sub> )	Wolff et al. 1979 MMAD 0.8
14	Gn Pig (Hartley)	8 hr (WB)				109 (5/16 died)	Wolff et al. 1979 MMAD 0.4
15	Rabbit (NS)	3.5 hr (WB)				1470 (1/2 died)	Treon et al. 1950 diameter 1-2
16	Rabbit (NS)	7 hr (WB)				1610 (1/2 died)	Treon et al. 1950 diameter 1-2

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
17	Rabbit (NS)	5 d 7 hr/d (WB)				383 (2/2 died)	Treon et al. 1950 diameter 1-2
<b>Systemic</b>							
18	Human-a	1 hr (WB)	Resp	0.1			Anderson et al. 1992 MMAD 1
19	Human-a	16 min (MO)	Resp	3			Aris et al. 1991 VMD 0.4, 6
20	Human-a	1 hr (WB)	Resp	0.396	0.999 (3.5% increased specific airway resistance, 4% decreased FEV <sub>1</sub> )	0.999 (eye irritation)	Avol et al. 1988 MMD 0.9
			Ocular	0.396			
21	Human-a	1 hr (WB)	Resp	0.127			Avol et al. 1990 MMAD 0.5
22	Human-a	3 hr (WB)	Resp	0.107			Frampton et al. 1995 MMAD 0.64
23	Human-a	40-45 min (MO)	Resp		0.07 (transient decrease in forced vital capacity and FEV <sub>1</sub> )		Hanley et al. 1992 MMAD 0.72

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
24	Human-a	50 min (MO or FA)	Resp		0.1	(35-45% increased respiratory resistance, 16-22% decreased maximum flow at 50% and 75% of VC, 7-8% decreased FEV <sub>1</sub> )	Koenig et al. 1985 MMAD 0.6
25	Human-a	45, 90 min (MO)	Resp	0.07			Koenig et al. 1992 MMAD 0.6
26	Human-a	40 min (MO)	Resp	0.07			Koenig et al. 1993 MMAD 0.6
27	Human-a	1 hr (WB)	Resp	0.41			Linn et al. 1986 MMAD 0.6
28	Human-a	2 d 6.5 hr/d (WB)	Resp	0.1			Linn et al. 1994 MMAD 0.5
29	Human-a	16 min (MO)	Resp	0.1	0.45	(15% decreased specific airway conductance at rest)	Utell et al. 1983 MMAD 0.8
30	Human-a	30 min (MO)	Resp		0.35	(19% reduction FEV <sub>1</sub> , 47% reduction in maximum expiratory flow rates at 60% total lung capacity)	Utell et al. 1989 MMAD 0.8

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
31	Human-n	5-15 min (FA)	Resp		0.35 M (35% increase in respiration rate, 20% decrease in maximum flow rates)		Amdur et al. 1952b mean particle size 1
32	Human-n	1 hr (WB)	Resp	1.578			Avol et al. 1988 MMD 0.9
33	Human-n	1 hr (H)	Resp	0.471 M			Bowes et al. 1995 MMAD 10
			Cardio	0.471 M			
34	Human-n	4hr (IC)	Resp	0.1 M			Chaney et al. 1980 MMD 0.5
			Hepatic Hemato	0.1 M 0.1 M			
35	Human-n	2 hr (WB)	Resp	1			Frampton et al. 1992 MMAD 0.9
36	Human-n	2 hr (WB)	Resp	1.2 M			Horvath et al. 1987 MMD 0.05
37	Human-n	4 hr (WB)	Resp	0.1			Kulle et al. 1982 MMD 0.13
38	Human-n	4 d 60 min/d (H)	Resp		0.471 M (increased tracheal and lung clearance of 3.4 micrometer particles)		Laube et al. 1993 MMAD 10.3

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
39	Human-n	1 hr (N)	Resp	0.33	0.98	(decreased bronchial clearance of 7.6 micrometer particles)	Leikauf et al. 1981 MMD 0.5
40	Human-n	1 hr (N)	Resp		0.108	(decreased bronchial clearance of 4.2 micrometer particles)	Leikauf et al. 1984 MMD 0.5
41	Human-n	2 hr (MO)	Resp		1	(15% increased bronchial clearance of 3 micrometer particles)	Newhouse et al. 1978 MMD 0.5
42	Human-n	1-2 hr (N)	Resp		0.1 M	(reduced rate of bronchial mucociliary clearance of 5.2 micrometer particles)	Spektor et al. 1989 MMAD 0.5
43	Human	8 hr (occup)	Resp	0.18 M			Gamble et al. 1984a MMAD 5
44	Rat (Fischer- 344)	5 d NS hr/d (WB)	Resp	100 M			Cavender et al. 1977 MMD 0.7-0.9
45	Rat (Fischer- 344)	4 hr (WB)	Resp		94.1 F	(increased thickness of mucus layer)	Lee et al. 1995 MMD 0.8
46	Rat (Sprague-Dawley)	7 d 23.5 hr/d (WB)	Resp	1.29 M			Warren and Last 1987 MMAD 0.4

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
47	Mouse CF-1	Gd 6-15 7 hr/d (WB)	Resp	20 F			Murray et al. 1979 CMD 1.6, 2.4
			Hepatic Bd Wt	20 F 20 F			
48	Gn Pig (NS)	1 hr (H)	Resp		1.9 (resistance increased about 1.5-fold)		Amdur 1958 MMD 0.8
49	Gn Pig (NS)	1 hr (H)	Resp		2.3 (resistance increased about 1.4-fold)	43.6 (resistance increased about 4.2-fold, increased lung weights, edema)	Amdur 1958 MMD 2.5
50	Gn Pig (NS)	1 hr (H)	Resp		30.5 (resistance increased about 1.4-fold)		Amdur 1958 MMD 7
51	Gn Pig (NS)	1 hr (H)	Resp		0.1 (resistance increased 41%, compliance decreased 27%)		Amdur et al. 1978 MMD 0.3
52	Gn Pig (NS)	1 hr (H)	Resp		0.11 (resistance increased 14%)		Amdur et al. 1978 MMD 1
53	Gn Pig (Hartley)	4hr (IC)	Resp			32.6 F (dyspnea, cyanosis, and lung injury)	Brownstein 1980 MMAD 1
54	Gn Pig (Hartley)	5 d NS hr/d (WB)	Resp		10F (diffuse regional alveolitis)		Cavender et al. 1977 MMD 0.7-0.9

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency/ (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
55	Gn Pig (Hartley)	1 or 4 d 3 hr/d (N)	Resp		0.3 M (increased beta-glucuronidase, lactate dehydrogenase, and total protein in lung lavage fluid)		Chen et al. 1992a MMD 0.3
56	Gn Pig (Hartley)	1 or 4 d 3 hr/d (N)	Resp		0.3 M (increased protein, lactate dehydrogenase and β-glucuronidase in lung lavage fluid)		Chen et al. 1992a MMD 0.04
57	Gn Pig (Hartley)	1 hr (H)	Resp	0.03 M	0.2 M (increased airway responsiveness to acetylcholine)		Chen et al. 1992b MMD 0.06
58	Gn Pig (Hartley)	2 d 6 hr/d (WB)	Resp			25 (edema and hemorrhage in the lungs)	Cockrell et al. 1978 MMD 1
59	Gn Pig (Hartley)	3, 7, or 14 d 24 hr/d (WB)	Resp	1 M	3.2 M (transient decrease and increase in airway responsiveness to inhaled histamine)		Kobayashi and Shinozaki 1993 MMAD 0.5
60	Gn Pig (Hartley)	4 hr (WB)	Resp			43.4 F (increased thickness of tracheal mucus layer, pulmonary edema in some guinea pigs)	Lee et al. 1995 MMD 0.93
61	Gn Pig (Hartley)	1 hr (N)	Resp			52 M (labored breathing, transient increased reactivity to substance P)	Stengel et al. 1993 MMAD 0.8-1.2

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)	
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
62	Gn Pig (Hartley)	8 hr (WB)	Resp			17.4	(labored breathing, hyperinflated lungs, hemorrhage and transudation of the lungs)	Wolff et al. 1979 MMAD 0.8
63	Gn Pig (Hartley)	8 hr (WB)	Resp			37.2	(hyperinflated lungs and labored breathing)	Wolff et al. 1979 MMAD 0.4
64	Rabbit (New Zealand)	3 hr (N)	Resp	0.05 M	0.075 M (increased responsiveness of bronchial rings to acetylcholine and histamine)			El-Fawal and Schlesinger 1994 MMD 0.3
65	Rabbit (New Zealand)	Gd 6-18 7 hr/d (WB)	Resp  Hepatic Bd Wt	5 F  20 F 20 F	20F (subacute rhinitis and tracheitis in dams)			Murray et al. 1979 CMD 1.6, 2.4
66	Rabbit (New Zealand)	14 d 0.5-4 hr/d (WB)	Resp		0.05 (decreased clearance from the respiratory region of 3.5 micrometer particles)			Schlesinger 1990a MMAD 0.3
67	Rabbit (New Zealand)	1 hr (N)	Resp		0.25 M (accelerated clearance of 3.5 micrometer particles from the alveolar region)			Schlesinger and Gearhart 1986 MMD 0.3
68	Rabbit (New Zealand)	1 hr (MO)	Resp	0.1 M	0.2 M (increased mucociliary clearance of 4.5 micrometer particles)			Schlesinger et al. 1984 MMAD 0.3

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
69	Rabbit (New Zealand)	3 hr (N)	Resp	0.125 M			Schlesinger et al. 1992b MMD 0.3
70	Rabbit (New Zealand)	2 hr (N)	Resp	0.5 M			Zelikoff and Schlesinger 1992 MMD 0.3
71	Rabbit (New Zealand)	4 d 2 hr/d (N)	Resp	0.75 M	1M (increased lactate dehydrogenase and protein in lung lavage fluid 24 hours after the last exposure)		Zelikoff et al. 1994 MMD 0.3
72	Ferret (NS)	4 hr (N)	Resp	0.5 F	1F (significantly accelerated clearance from the lungs of 1.9 micrometer particles)		Mannix et al. 1991 MMAD 0.3
<b>Immunological/Lymphoreticular</b>							
73	Human-n	2 hr (WB)		1			Frampton et al. 1992 MMAD 0.9
74	Mouse (CD-1)	1 or 5 d 2 hr/d (H)		0.543 F			Grose et al. 1982 VMD <0.1
75	Gn Pig (Hartley)	1 or 4 d 3 hr/d (N)		0.3 M			Chen et al. 1992a MMD 0.3

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
76	Gn Pig (Hartley)	1 or 4 d 3 hr/d (N)			0.3 M (decreased phagocytic activity of alveolar macrophages)		Chen et al. 1992a MMD 0.04
77	Gn Pig (Hartley)	2 wk continuous (WB)		0.3 M	1 M (enhancement of antigen-induced histamine release by mast cells)		Fujimaki et al. 1992 MMD 0.55-0.73
78	Gn Pig (Hartley)	3 hr or 5 d 3 hr/d (WB)			0.969 M (15.6-23.3% reduced intracellular pH in alveolar macrophages)		Qu et al. 1993 MMD 0.3
79	Rabbit (New Zealand)	3 hr (N)		0.05 M	0.125 M (decreased pH of alveolar macrophages)		Chen et al. 1995 MMD 0.3
80	Rabbit (New Zealand)	13 d 2 hr/d (N)			0.5 M (increased phagocytic activity of alveolar macrophages at day 3, decreased by day 14)		Schlesinger 1987 MMD 0.3
81	Rabbit (New Zealand)	5 d 1 hr/d (WB)		0.5 M	1 M (decreased phagocytic activity of alveolar macrophages)		Schlesinger et al. 1990a MMD 0.3
82	Rabbit (New Zealand)	3 hr (N)		0.05 M	0.075 M (effects on macrophages: decreased phagocytic activity, production of superoxide anion, tumor necrosis factor activity)		Schlesinger et al. 1992b MMD 0.3

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure	Species <sup>a</sup> (strain)	Exposure duration/frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
83	Rabbit (New Zealand)	2 h (N)		0.05 M	0.075 M (effects on macrophages: decreased tumor necrosis factor cytotoxic activity, decreased superoxide anion production)		Zelikoff and Schlesinger 1992 MMD 0.3
84	Rabbit (New Zealand)	4 d 2 hr/d (N)		0.5 M	0.75 M (suppressed macrophage-mediated immunity)		Zelikoff et al. 1994 MMD 0.3
<b>Neurological</b>							
85	Human-a	1 hr (WB)		0.396	0.999 (increased report of fatigue and headaches)		Avol et al. 1988 MMD 0.9
86	Human-n	1 hr (WB)		1.578			Avol et al. 1988 MMD 0.9
<b>Reproductive</b>							
87	Mouse CF-1	Gd 6-15 7 hr/d (WB)		20 F			Murray et al. 1979 CMD 1.6, 2.4
88	Rabbit (New Zealand)	Gd 6-18 7 hr/d (WB)		20 F			Murray et al. 1979 CMD 1.6, 2.4
<b>Developmental</b>							
89	Mouse CF-1	Gd 6-15 7 hr/d (WB)		20			Murray et al. 1979 CMD 1.6, 2.4

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m3)	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m3)	Serious (mg/m3)	
90	Rabbit (New Zealand)	Gd 6-18 7 hr/d (WB)		20			Murray et al. 1979 CMD 1.6, 2.4
<b>INTERMEDIATE EXPOSURE</b>							
<b>Systemic</b>							
91	Gn Pig (NS)	32-139 d continuous (WB)	Resp	2	25	(mild histopathologic changes in the lungs including edema)	Thomas et al. 1958 mean diameter 0.5
92	Gn Pig (NS)	32-139 d continuous (WB)	Resp		2	(mild histopathologic changes in the lungs including edema)	Thomas et al. 1958 mean diameter 0.9
93	Gn Pig (NS)	32-139 d continuous (WB)	Resp		2	(mild histopathologic changes in the lungs including edema, histopathological changes in the upper respiratory tract)	Thomas et al. 1958 mean diameter 4
94	Dog (Beagle)	225 d 21 hr/d (WB)	Resp		0.755	(15% decreased carbon monoxide diffusion capacity)	Lewis et al. 1969 90% <0.5
95	Rabbit (New Zealand)	4 or 8 mo 5 d/wk 1 hr/d (N)	Resp		0.25 M	(increased bronchial sensitivity to acetylcholine)	Gearhart and Schlesinger 1986 MMD 0.3

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
96	Rabbit (New Zealand)	57 or 240 d 5 d/wk 1 hr/d (N)	Resp		0.25 M (accelerated clearance of 3.5 micrometer particles from the alveolar region)		Schlesinger and Gearhart 1986 MMD 0.3
97	Donkey (NS)	6 mo 5 d/wk 1 hr/d (N)	Resp		0.106 (erratic and slower bronchial clearance of 5 micrometer ferric oxide particles)		Schlesinger et al. 1979 MMAD 0.5
<b>Immunological/Lymphoreticular</b>							
98	Gn Pig (Hartley)	4 wk continuous (WB)		1 M	3.2 M (suppression of A23187-induced histamine release by mast cells)		Fujimaki et al. 1992 MMD 0.55-0.73
<b>CHRONIC EXPOSURE</b>							
<b>Systemic</b>							
99	Human	1->15 yr (occup)	Resp	12.6 M			El-Sadik et al. 1972 NS
			Other		12.6 M (lowered saliva pH; erosion of teeth in 39.4%)		
100	Human	average 12.2 yr (occup)	Resp	0.1	0.21 (5% decrease in forced vital capacity)		Gamble et al. 1984b NS
			Other	0.1	0.21 (prevalence of tooth etching and erosion 37.9% compared to 7.9% at the lower concentration)		

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
101	Human	9 yr (environ)	Resp			0.8 (bronchitis, pulmonary emphysema, sore throat)	Kitagawa 1984 MMD 0.7-3.3
102	Human	max 4.5 yr (occup)	Resp	0.5 M			Kremer et al. 1994 NS
103	Human	NS (occup)	Other		3M (erosion of the teeth)		Malcolm and Paul 1961 NS
104	Human	few d to >40 yr (occup)	Resp		1.4 M (slight increase in bronchitis)		Williams 1970 NS
105	Monkey (Cynomol- gus)	78 wk 7 d/wk 23.3 hr/d (WB)	Resp	0.48	4.79 (moderate to severe bronchiolar epithelial hypertrophy and hyperplasia, thickening of respiratory bronchioles in 9/9, no change in arterial oxygen)		Alarie et al. 1973 MMD 0.54, 0.7
			Cardio	4.79			
			Hemato	4.79			
			Hepatic	4.79			
			Renal	4.79			
			Bd Wt	4.79			

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to <sup>a</sup> figure	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)	
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )		
106	Monkey (Cynomol- gus)	78 wk 7 d/wk 23.3 hr/d (WB)	Resp		0.38	(slight bronchiolar epithelial hyperplasia in 5/9, slight thickening of the walls of the respiratory bronchioles in 3/9, no change in arterial oxygen)	2.43	Alarie et al. 1973 MMD 2.15, 3.6
			Cardio	2.43				
			Hemato	2.43				
			Hepatic	2.43				
			Renal	2.43				
			Bd Wt	2.43				
107	Gn Pig (Hartley)	52 wk 7 d/wk 23 hr/d (WB)	Resp	0.1				Alarie et al. 1973 MMD 2.78
			Cardio	0.1				
			Hemato	0.1				
			Hepatic	0.1				
			Renal	0.1				
			Bd Wt	0.1				
108	Gn Pig (Hartley)	52 wk 7 d/wk 23 hr/d (WB)	Resp	0.08				Alarie et al. 1973 MMD 0.84
			Cardio	0.08				
			Hemato	0.08				
			Hepatic	0.08				
			Renal	0.08				
			Bd Wt	0.08				

Table 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (continued)

Key to figure <sup>a</sup>	Species (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/m <sup>3</sup> )	LOAEL		Reference aerosol size (μm)
					Less serious (mg/m <sup>3</sup> )	Serious (mg/m <sup>3</sup> )	
109	Gn Pig (Hartley)	52 wk 5 d/wk 23 hr/d (WB)	Resp	0.9			Alarie et al. 1975 MMD 0.49
			Cardio	0.9			
			Hemato	0.9			
			Hepatic	0.9			
			Renal	0.9			
			Bd Wt	0.9			
110	Rabbit (New Zealand)	1 yr 5 d/wk 2 hr/d (N)	Resp		0.125 M (decreased clearance of 4.5 micrometer particles during 6 month recovery period)		Schlesinger et al. 1992a MMD 0.3
			Bd Wt	0.125 M			

<sup>a</sup>The numbers correspond to entries in Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; CMD = count median diameter; d = day(s); F = female; FEV<sub>1</sub> = forced expiratory volume in 1 second; (FA) = face-mask; Gn Pig = guinea pig; Gd = gestation day; (H) = head-only; Hemato = hematological; hr = hour(s); Human-a = asthmatic; Human-n = normal; LC<sub>50</sub> = lethal concentration 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; max = maximum; μm = micrometer; min = minute(s); MMAD = mass median aerodynamic diameter; MMD = mass median diameter; mo = month(s); (MO) = mouth only; (N) = nose-only; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; VC = vital capacity; VMD = volume median diameter; (WB) = whole-body; wk = week(s); yr = year(s)

**Figure 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation**  
**Acute ( $\leq 14$  days)**

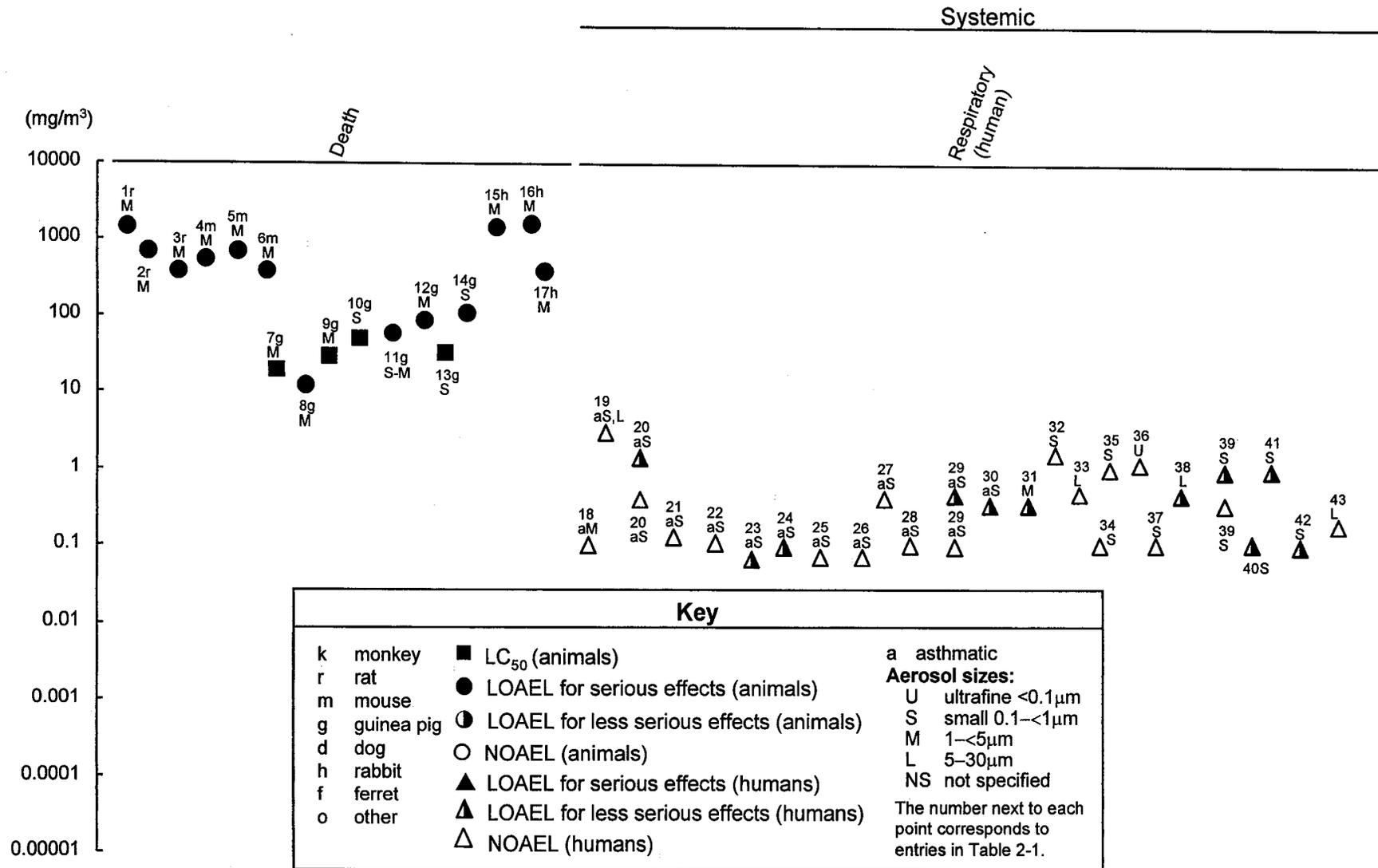
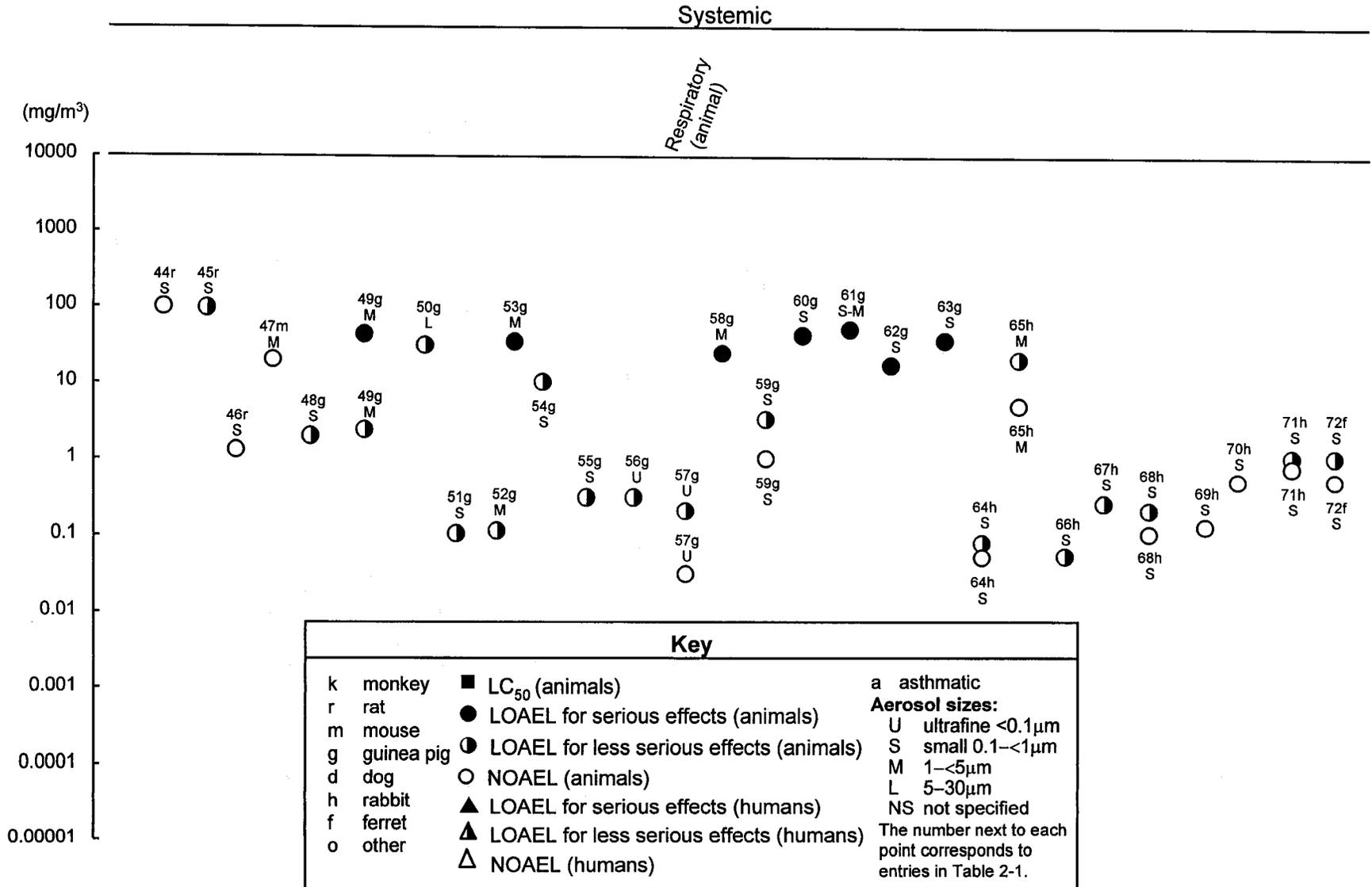
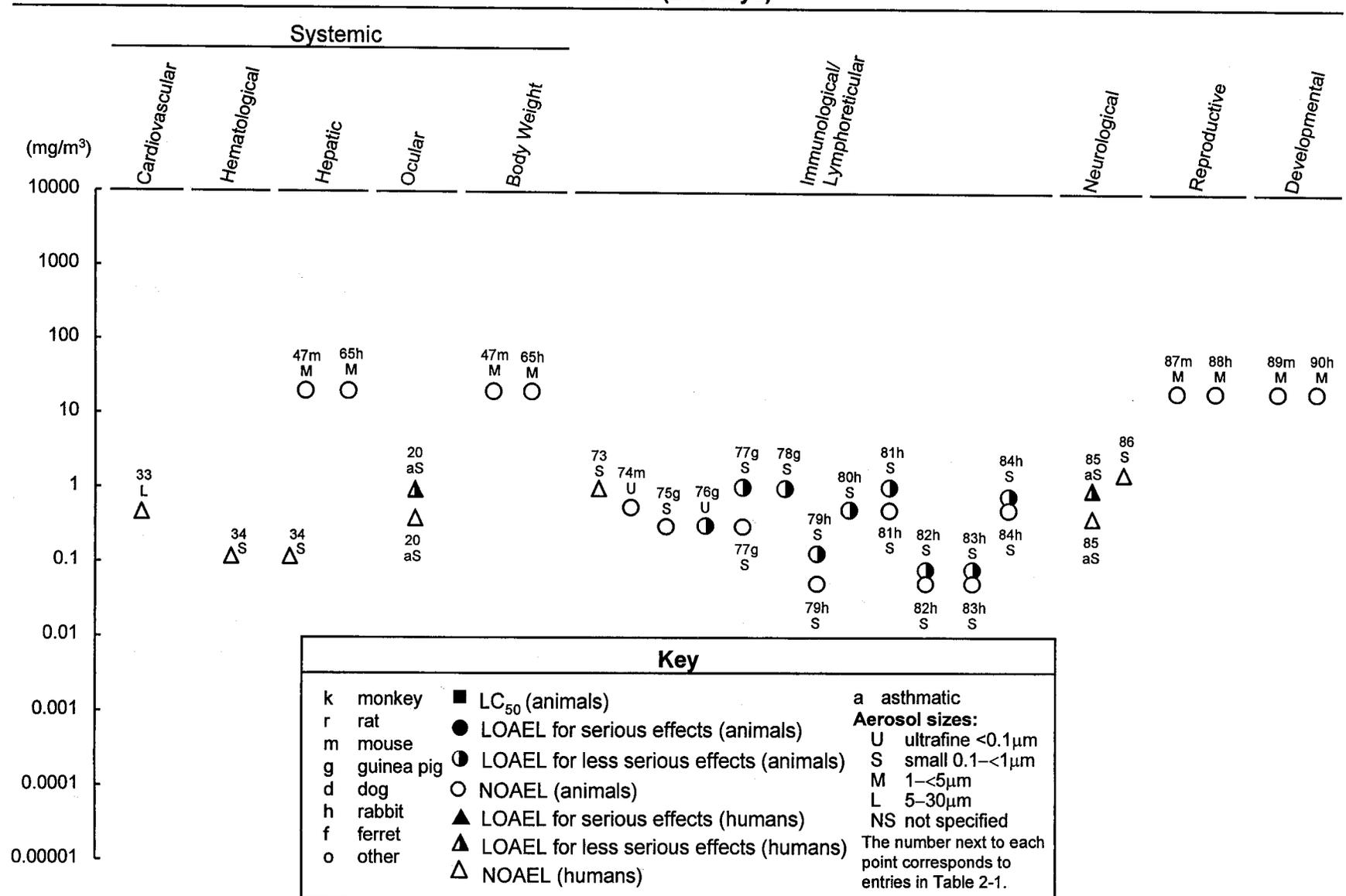


Figure 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (cont.)

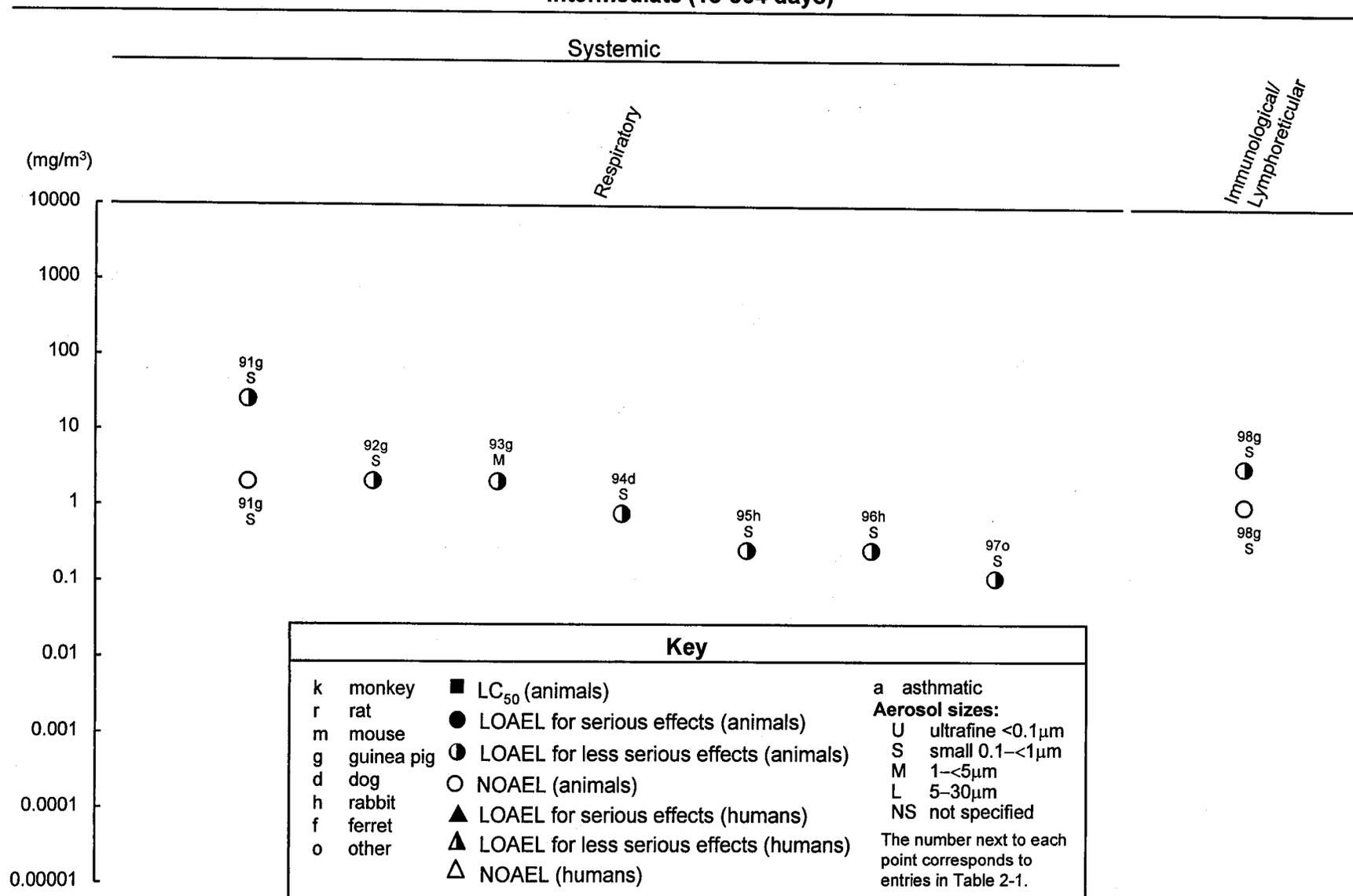
Acute ( $\leq 14$  days)



**Figure 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (cont.)**  
**Acute ( $\leq 14$  days)**

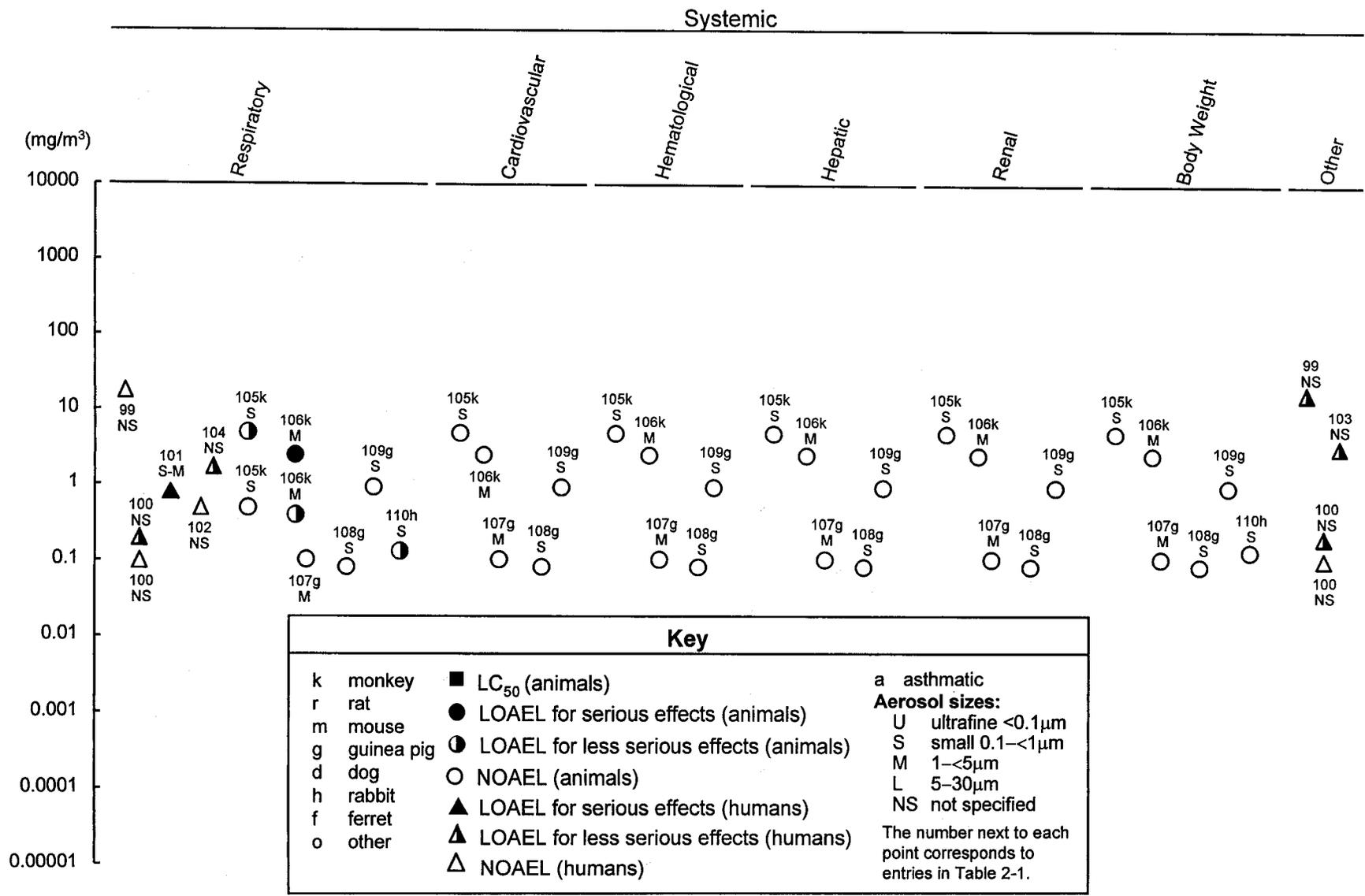


**Figure 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (cont.)**  
**Intermediate (15-364 days)**



**Figure 2-1. Levels of Significant Exposure to Sulfuric Acid - Inhalation (cont.)**

Chronic (≥365 days)



## 2. HEALTH EFFECTS

No studies were located regarding gastrointestinal, musculoskeletal, or dermal effects in humans or animals after inhalation exposure to sulfur trioxide or sulfuric acid.

**Respiratory Effects.** Respiratory tract irritation was noted by 12 persons working next to a chemical plant that emitted sulfur trioxide (Stueven et al. 1993). The subjects were exposed to an unspecified concentration for approximately 2 hours, and 9 of 12 subjects went to the hospital. The symptoms reported included pleuritic chest pain in two subjects, chest tightness in three subjects, vague chest discomfort in one subject, cough in one subject, and an acidic taste in the mouth and nasal irritation in one subject. All subjects were asymptomatic 6 hours after the exposure when they were released from the hospital. Adult respiratory distress syndrome was reported in a man accidentally exposed to high concentrations of sulfuric acid fumes (Knapp et al. 1991). Effects noted upon initial hospital admission included hypotension and a crackling sound from his lungs. A chest X-ray revealed diffuse confluent opacities consistent with chemical pneumonia. Less than 24 hours later, a chest X-ray revealed a pneumomediastinum and a right pneumothorax. After 12 days in the hospital he was released feeling weak but without a cough or exertional dyspnea. After 3 days at home he returned to the hospital with an abscess in his lung. He was treated with antibiotics and released after 1 week. No permanent deficits in lung function were noted.

A case was also reported of a previously healthy 40-year old male worker who was accidentally sprayed in the face with 35% fuming sulfuric acid (equivalent to 108.04% sulfuric acid) (Goldman and Hill 1953). Immediately after the accident, the man rinsed himself off in a safety shower for eight minutes, during which time he inhaled sulfuric acid mists and vapors. Acute respiratory symptoms included difficulty breathing and cough with the production of bloody sputum. Moist rales were audible in both lungs and X-rays revealed pulmonary congestion and inflammation. Pulmonary damage was permanent and was characterized by chronic cough, difficulty breathing, reduced respiratory performance, and bronchiectasis. Fibrosis and emphysema developed within a 7-18 month period.

Numerous studies are available regarding lung function in volunteers (healthy and asthmatic) exposed to sulfuric acid aerosols for short periods of time. In these studies lung function is often assessed using spirometry, which measures lung volumes and flows. Spirometric methods require subject cooperation and effort. Some of the most frequent measurements reported are forced vital capacity (FVC), forced expiratory volume in 1 second ( $FEV_1$ ), and forced expiratory volume at 50% or 75% ( $FEV_{50\%}$ ,  $FEV_{75\%}$ ). FVC is the volume (in liters) of air that can be exhaled forcefully and rapidly after a maximal inspiration.  $FEV_1$  is the volume of air that can be forcefully exhaled in 1 second.  $FEV_{50\%}$  and  $FEV_{75\%}$  are the volumes at 50% and

## 2. HEALTH EFFECTS

75% of the FEV curves (EPA 1994). Additional lung function tests can be completed using a whole-body plethysmograph. With this method, specific airway resistance ( $SR_{aw}$ ), the product of airway resistance and thoracic gas volume, can be determined.

The effect of relative humidity on sulfuric acid-induced respiratory tract symptoms has been studied. Twelve normal male volunteers were exposed to  $39.4 \text{ mg/m}^3$  sulfuric acid aerosols at a relative humidity of 62% for 1 hour, or to  $20.8 \text{ mg/m}^3$  at a relative humidity of 91% for 30 minutes (Sim and Pattle 1957). The MMD for both humidity conditions was 0.99  $\mu\text{m}$ . The exposure at 62% relative humidity was well tolerated. There was some coughing on entering the chamber, which wore off within a few minutes. Resistance to airflow was increased 36-100% above normal in all 12 exposed subjects. At a relative humidity of 91%, the study authors indicated that the ‘mist was almost intolerable at the onset but the men were able to continue for a period of 30 minutes.’ Intense coughing was observed throughout the experimental period, and resistance to air flow was increased 43-150%. The study authors note that during the chamber exposures, the men were “allowed to walk around or smoke if they wished.” Because exposure conditions were not well controlled, this study is not presented in Table 2-1 or Figure 2-1.

The pattern of respiration was studied in an unspecified number of normal male volunteers exposed to sulfuric acid aerosols (mean particle size 1  $\mu\text{m}$ ) with a face mask for 5-15 minutes at  $0.35\text{-}5 \text{ mg/m}^3$  (Amdur et al. 1952b). Changes in respiration were observed at all concentrations. At  $0.35 \text{ mg/m}^3$ , a 35% increase in respiration rate and a 20% decrease in maximum flow rate occurred and continued throughout the exposure period. At  $5 \text{ mg/m}^3$ , the major response was a decrease in minute volume.

No effects on minute volume, tidal volume, respiratory frequency, or minute ventilation were noted in 7 healthy male volunteers exposed to  $0.471 \text{ mg/m}^3$  sulfuric acid (MMAD 10  $\mu\text{m}$ ) for 1 hour using a head dome (Bowes et al. 1995). The 1-hour exposure consisted of 40 minutes of rest, followed by 20 minutes of moderately heavy exercise. The 10- $\mu\text{m}$  aerosol size used in this study would not reach the lungs without oral breathing. In a 2-hour exposure study, no effects on pulmonary function were observed in 9 normal male subjects exposed to  $1.2\text{-}1.6 \text{ mg/m}^3$  sulfuric acid (MMD 0.05  $\mu\text{m}$ ) with intermittent exercise (Horvath et al. 1987). Additional acute-duration exposures of normal humans have also not caused any adverse effects on pulmonary function tests (Anderson et al. 1992; Avol et al. 1988; Frampton et al. 1992; Koenig et al. 1993; Kulle et al. 1982; Laube et al. 1993; Leikauf et al. 1981, 1984; Linn et al. 1994; Newhouse et al. 1978; Stacy et al. 1983; Utell et al. 1984). All of the studies, except those by Leikauf et al. (1981, 1984) and Utell et al. (1984), used intermittent periods of exercise during exposure periods that lasted from 16 minutes to 4 hours.

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Studies of both normal and asthmatic subjects indicate that asthmatics are more sensitive to sulfuric acid exposures. A concentration-related increase in specific airway resistance ( $SR_{aw}$ ) was observed in asthmatics (12 men, 9 women) exposed to sulfuric acid aerosols (MMD 0.9  $\mu\text{m}$ ) at 0, 0.396, 0.999, and 1.46  $\text{mg}/\text{m}^3$  for 1 hour with three 10-minute exercise periods (Avol et al. 1988). The effect was significant at 0.999  $\text{mg}/\text{m}^3$ , and the lowest concentration is considered a NOAEL. No effects on pulmonary function were observed in normal subjects (14 men, 7 women) exposed to sulfuric acid aerosols at concentrations as high as 1.578  $\text{mg}/\text{m}^3$  (Avol et al. 1988). Self-reported respiratory symptoms also showed a concentration-related increase in asthmatics, with no clear effect in normal subjects.

Decreased specific airway conductance was observed in 17 asthmatics exposed to sulfuric acid aerosols (MMAD 0.8  $\mu\text{m}$ ) through a mouthpiece at 0.45  $\text{mg}/\text{m}^3$ , while at rest for 16 minutes (Utell et al. 1983). At a concentration of 1  $\text{mg}/\text{m}^3$ , a reduction in  $FEV_1$  was also observed. No effects on pulmonary function were observed when these subjects were exposed to 0.1  $\text{mg}/\text{m}^3$ . Reductions in  $FEV_1$  and maximum expiratory flow rates at 60% of total lung capacity were observed in 15 asthmatic volunteers exposed to sulfuric acid aerosols (MMAD 0.8  $\mu\text{m}$ ) through a mouthpiece at 0.35  $\text{mg}/\text{m}^3$  for 30 minutes (Utell et al. 1989). The response was greater when the subjects reduced ammonia concentrations in the mouth (tooth brushing, gargling with citrus juice) just before the exposure.

Acute-duration exposure studies of volunteers indicate that adolescent asthmatics are generally more sensitive to inhalation of sulfuric acid aerosols than healthy older individuals. In a study of 22 adolescent (age 12-19) asthmatics exposed to 0.07  $\text{mg}/\text{m}^3$  sulfuric acid aerosols (MMAD 0.71  $\mu\text{m}$ ) through a mouthpiece, transient decreases in FVC and  $FEV_1$  were observed (Hanley et al. 1992). During the 4045-minute exposures, the subjects exercised for 10 or 30 minutes. The investigators indicated that the response was small and was no longer significant 20 minutes after the end of the exposure. No effects on maximal flow at 50% or 75% of expired vital capacity or on total respiratory resistance were observed. Self-reported respiratory symptoms were not consistently related to exposure. Increased respiratory resistance, decreased maximum flow at 50% and 75% of vital capacity, and decreased  $FEV_1$  were observed in 10 asthmatic adolescents exposed to 0.1  $\text{mg}/\text{m}^3$  sulfuric acid (MMAD 0.6  $\mu\text{m}$ ) through a mouthpiece while wearing noseclips or through a face mask that allowed oronasal breathing (Koenig et al. 1985). Exposures were for 30 minutes at rest, followed by 20 minutes with moderate exercise. There were no statistically significant differences in pulmonary function between the two methods of exposure. A significant ( $p=0.03$ ) decrease in  $FEV_1$  of 6.1% was observed in 14 adolescent asthmatics that were exposed to 0.035  $\text{mg}/\text{m}^3$  sulfuric acid (MMAD 0.6  $\mu\text{m}$ ) for 45 minutes (Koenig et al. 1992). During the exposures, the subjects exercised for alternating 15-minute

## 2. HEALTH EFFECTS

periods. No significant effects on lung function were observed after 90 minutes of exposure at  $0.035 \text{ mg/m}^3$ , or after 45 or 90 minutes of exposure at a concentration of  $0.07 \text{ mg/m}^3$ . Therefore, the  $0.07\text{-mg/m}^3$  concentration is presented as a NOAEL in Table 2-1 and Figure 2-1. Lung function, assessed by measuring  $\text{SR}_{\text{aw}}$  and  $\text{FEV}_1$ , was not affected in exercising asthmatic volunteers (20 male and 12 female, age 6-16) exposed to sulfuric acid aerosols (MMAD  $0.5 \mu\text{m}$ ) oronasally at up to  $0.127 \text{ mg/m}^3$ , or orally at  $0.134 \text{ mg/m}^3$  for 1 hour (Avol et al. 1990). The study authors noted that in 1 subject,  $\text{SR}_{\text{aw}}$ , increased by  $14.2 \text{ cm H}_2\text{O-second}$  during the oronasal study, and by  $8.4 \text{ cm H}_2\text{O-second}$  in the oral study, suggesting that there may be an acid-sensitive subpopulation of young asthmatics.

Exposure of 9 asthmatic and 8 healthy seniors (age 60-75) to  $0.07 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.6 \mu\text{m}$ ) through a mouthpiece while wearing noseclips (30 minutes at rest, 10 minutes of exercise) did not have any significant effects on FVC,  $\text{FEV}_1$ , or total respiratory resistance in either group of subjects (Koenig et al. 1993). No effects on  $\text{SR}_{\text{aw}}$  were observed in 9 asthmatics exposed to sulfuric acid aerosols for 16 minutes through a mouthpiece at  $3 \text{ mg/m}^3$  using aerosols of VMDs of  $0.4$  or  $6 \mu\text{m}$  (Arks et al. 1991). Exposure of 10 asthmatics to  $1.4 \text{ mg/m}^3$  sulfuric acid aerosols (VMD  $6 \mu\text{m}$ ) for 1 hour with exercise during alternating 15-minute periods also had no effect on  $\text{SR}_{\text{aw}}$  (Aris et al. 1991). Compared to exercise in clean air, no effects on  $\text{SR}_{\text{aw}}$  or forced expiratory function were observed in 27 asthmatics exposed to  $0.41 \text{ mg/m}^3$  sulfuric acid aerosols (MMAD  $0.5 \mu\text{m}$ ) in a chamber for 1 hour with alternating 10-minute periods of exercise (Linn et al. 1986).

Compared to exposure to sodium chloride aerosols ( $0.105 \text{ mg/m}^3$ ; MMAD  $0.64 \mu\text{m}$ ), a 3-hour exposure of 30 asthmatic or 30 normal volunteers to  $0.107 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.64 \mu\text{m}$ ) had no significant effects on FVC or  $\text{FEV}_1$  (Frampton et al. 1995). During the exposures, the subjects exercised intermittently. Changes in pulmonary function tests (thoracic gas volume, airway resistance, FVC,  $\text{FEV}_1$ , specific airway conductance) were not observed in 12 normal volunteers immediately after and 18 hours after a 2-hour exposure to  $1 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.9 \mu\text{m}$ ) (Frampton et al. 1992). Bronchoscopy, completed 18 hours after the exposure, did not reveal any effects on the appearance of the airways or the bronchial mucosa. Collection of bronchial secretions from these subjects for 12 hours after sodium chloride or acid exposure did not reveal any changes in airway mucin glycoproteins or other closely associated proteins (Culp et al. 1995).

Changes in  $\text{SR}_{\text{aw}}$ , FVC, and  $\text{FEV}_1$ , were not observed in 30 asthmatic or 15 normal subjects exposed to  $0.1 \text{ mg/m}^3$  sulfuric acid (MMAD  $1 \mu\text{m}$ ) for 6.5 hours per day for 2 days (Linn et al. 1994). The subjects

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exercised during the first 50 minutes of each exposure hour and then rested for 10 minutes, during which pulmonary function tests were completed. Not all subjects were fit enough to exercise through six 50-minute periods. It is not stated whether these were normal or asthmatic subjects. In a study of asthmatic and normal volunteers exposed to  $0.1 \text{ mg/m}^3$  sulfuric acid aerosols (MMAD  $0.5 \text{ }\mu\text{m}$ ) for 1 hour with alternating 10-minute exercise periods, only 1 of 14 asthmatics responded with a fall in  $\text{FEV}_1$  during the first 15 minutes of exposure (Anderson et al. 1992). This study provides further evidence that there may be a subgroup of asthmatics that are more sensitive to sulfuric acid aerosol exposure.

The response to unbuffered sulfuric acid aerosols compared to glycine-buffered sulfuric acid aerosols, both at pH 2, was studied by Fine et al. (1987). The 8 asthmatic subjects were exposed to the aerosols (MMD  $5.3 \text{ }\mu\text{m}$ ) through a mouthpiece during 3 minutes of tidal breathing. The exposure concentration was not stated, but the nebulizer had a mean liquid water output of  $5.7 \text{ g/minute}$ .  $\text{SR}_{\text{aw}}$  was not increased after inhalation of unbuffered sulfuric acid at pH 2, while a  $>50\%$  increase was observed in 7 of 8 subjects exposed to the glycine-buffered sulfuric acid at pH 2. This study demonstrated that titratable acidity, which measures total available hydrogen ion level, has a greater effect on bronchoconstriction than pH, which measures total free hydrogen ion concentration. A longer duration of bronchoconstriction is also expected from buffered acids because of a gradual release of available hydrogen ion.

A number of human exposure studies suggest that exposure to sulfuric acid aerosols may have more of an effect on clearance of particles than on pulmonary function tests. The results reported in these studies are not only dependent on the sulfuric acid aerosol size but also on the size of the test particles. The aerodynamic size and density of the test particles determines where in the respiratory tract they will deposit. Sulfuric acid appears to have different effects on clearance in different regions of the respiratory tract. Enhanced clearance of a  $^{99\text{m}}$ technetium-tagged albumin saline aerosol (MMD  $3 \text{ }\mu\text{m}$ ) was noted in 10 humans exposed by mouth to  $1 \text{ mg/m}^3$  sulfuric acid aerosol (MMD  $0.5 \text{ }\mu\text{m}$ ) for 2 hours (Newhouse et al. 1978). Compared to exposure to water mist, bronchial clearance 2 hours after the exposure was increased by about 15%. Exposure to  $1 \text{ mg/m}^3$  sulfuric acid aerosol had no effects on vital capacity,  $\text{FEV}_1$ , or  $\text{FEV}_{50\%-75\%}$ . The study authors cautioned that enhanced bronchial clearance should not be considered a beneficial effect, and they attributed the effect to a patho-physiological response of the airways to inhaled irritants. The authors also suggested that longer term exposure may decrease clearance.

Enhanced tracheal and lung clearance of  $3.4 \text{ }\mu\text{m}$   $^{99\text{m}}$  technetium-tagged sulfur colloid was observed in 7 men exposed to  $0.471 \text{ mg/m}^3$  sulfuric acid (MMAD  $10.3 \text{ }\mu\text{m}$ ) 60 minutes/day for 4 days (Laube et al. 1993).

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Pulmonary function tests were not affected in these subjects. The study authors indicated that the mechanism underlying the observed changes in clearance was not known.

In studies of clearance of  $^{99m}$  technetium-tagged ferric oxide particles, subjects were exposed nose only to ferric oxide particles at an MMD of 7.6  $\mu\text{m}$  (n=10) (Leikauf et al. 1981) or 4.2  $\mu\text{m}$  (n=8) (Leikauf et al. 1984), followed by nose-only exposure to sulfuric acid aerosols (MMD 0.5  $\mu\text{m}$ ) for 1 hour at about 0, 0.1, 0.3, or 1  $\text{mg}/\text{m}^3$ . No effects on tracheal mucociliary transport rate were noted for either particle size, but differences in bronchial clearance were observed. For the 7.6- $\mu\text{m}$  particles, a significant decrease ( $p<0.05$ ) in the mean bronchial clearance time, from 80 to 50 minutes, occurred in the low exposure group. However, in the high dose group, a significant increase ( $p<0.05$ ) in the mean bronchial clearance time, 118 minutes, was observed (Leikauf et al. 1981). The values were significantly different ( $p<0.05$ ) from air exposure at the low and high concentrations. The study authors noted two response patterns in the subjects of this study. Six persons with slower clearance had significant alterations in bronchial clearance, while four subjects with faster clearance did not respond to sulfuric acid aerosol exposure. For the 4.2- $\mu\text{m}$  particles, bronchial clearance half-times were 80, 110, 106, and 142 minutes at 0, 0.1, 0.3, and 1  $\text{mg}/\text{m}^3$ , respectively (Leikauf et al. 1984). The values were significantly reduced ( $p<0.05$ ) from air exposure at the low and high concentrations. In a comparison of their two studies, the authors stated that the inhibitory effect of the high concentration started sooner and lasted longer in the group inhaling the smaller radiolabelled ferric oxide particles. The high concentration had a greater effect on clearance from the tracheobronchial region compared to clearance from the nasopharyngeal region. After exposure to the low concentration, clearance half-time was longer than air exposure in the group inhaling the smaller ferric oxide particles, and faster than air exposure in the group inhaling the larger iron oxide particles. The low concentration decreased clearance in the tracheobronchial region and enhanced clearance in the nasopharyngeal region.

Slower clearance was also reported in 10 male volunteers exposed to 0.1  $\text{mg}/\text{m}^3$  sulfuric acid aerosols (MMAD 0.5  $\mu\text{m}$ ) for 1 or 2 hours (Spektor et al. 1989). The subjects were exposed to  $^{198}$ gold-tagged iron oxide before the sulfuric acid exposures and  $^{99m}$  technetium-tagged iron oxide particles after the exposures. Both labeled particles had a size of about 5.2  $\mu\text{m}$ . Clearance of the particles deposited after the exposure was slower compared to that of particles deposited before the sulfuric acid exposure. After 2 hours of exposure to sulfuric acid aerosols, the clearance half-time tripled compared to air exposure, and reduced clearance was still noted 3 hours after the end of the exposure. After 1 hour of exposure, clearance half-time was doubled compared to air exposure, and the reduced rate of clearance lasted for 2 hours after the exposure. The results of this study suggest a cumulative response of duration of exposure to sulfuric acid aerosols.

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In conclusion, several factors could explain the variability in results for the clearance studies. Clearance is affected by the location of respiratory deposition which depends on both the aerodynamic size and density of sulfuric acid droplets and test particles. Sulfuric acid appears to have different effects on clearance in different regions of the respiratory tract. Differences in exposure concentrations and times may also have varying effects on clearance.

In addition to experimental exposure studies in humans, the effect of sulfuric acid exposure has been studied after pollution episodes and following occupational exposure. Hospital admissions for respiratory effects in southern Ontario, Canada, were increased on days with high sulfate concentrations (Bates and Sizto 1987). This association was observed in the summer but not the winter. In an asthma episode in Japan in which more than 600 cases of chronic bronchitis, allergic asthma bronchitis, pulmonary emphysema, and sore throat were reported, measurements revealed the presence of acid mist particles and a sulfur trioxide/sulfur dioxide ratio of 0.48, indicative of sulfuric acid mist (Kitagawa 1984). The study authors concluded that the respiratory symptoms were a result of concentrated sulfuric acid mist with an MMD of 0.7-3.3  $\mu\text{m}$ . Concentrations of sulfuric acid were estimated to be 0.8-12.8  $\text{mg}/\text{m}^3$ . In a large study of nonsmokers in California, the development of asthma symptoms and severity of airway obstructive disease was significantly associated with ambient concentrations of sulfate (Abbey et al. 1993, 1995). However, correlation between levels of sulfates and total suspended particulates (TSPs) suggested that TSPs may have been responsible for the observed effects. Air pollution studies are limited because it is difficult to separate effects associated with various air pollutants.

In Uniontown, PA the association was examined between particle-strong acidity (extractable acidity from sulfate particles composed partially of sulfuric acid and ammonium bisulfate) and respiratory function in 4th and 5th grade children (60 asthmatic and 23 healthy) (Neas et al. 1995). When weighted for time spent outdoors, a 12-hour exposure to each 125  $\text{nmol}/\text{m}^3$  (0.012  $\text{mg}/\text{m}^3$  sulfuric acid) increase in particle-strong acidity was associated with a 2.5 L/min decrease in evening peak expiratory flow rate (PEFR) in asthmatic children. Incidence of cough in healthy and asthmatic children was also associated with particle-strong acidity levels. A second group of investigators attempted to simulate the Uniontown air pollution mixture in a chamber study of 41 children aged 9-12 years (15 healthy, 26 asthmatic or atopic) (Linn et al. 1997). With the exception of ozone, exposure to air pollutants (sulfuric acid with MMAD=0.6  $\mu\text{m}$  and sulfur dioxide) were three times the levels of Uniontown so that the total dose in 4 hours was equivalent to a 12 exposure of the Uniontown pollutant mixture. The ozone level could not be increased because a higher concentration would have resulted in irritation. Exposure to the air pollution mixture did not result in

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significant adverse effects on respiratory performance (FVC, FEV<sub>1</sub>, and PEF<sub>R</sub>). Possible reasons for the discrepancies between the two studies included differences in the composition of the air pollution mixture, differences in exposure time, and psychological effects of chamber exposure.

Lead-acid battery workers (n=225) were studied for evidence of changes in acute pulmonary function after an 8-hour shift (Gamble et al. 1984a). The average sulfuric acid exposure concentration was 0.18 mg/m<sup>3</sup>, with a range of 0.08-0.35 mg/m<sup>3</sup> (MMAD 5 μm). Lung function tests (FVC, FEV<sub>1</sub>, FEV<sub>50%</sub>, FEV<sub>75%</sub>) completed before and after the shift provided no evidence of acute pulmonary effects.

A slight increase in bronchitis was observed in 460 battery factory workers exposed to sulfuric acid aerosols at an average concentration of 1.4 mg/m<sup>3</sup> for up to 40 years (Williams 1970). No effects on FVC or FEV<sub>1</sub> were observed. A small decrease in FVC was observed in 248 workers exposed to an average sulfuric acid aerosol concentration of 0.21 mg/m<sup>3</sup> compared to workers exposed to an average concentration of 0.1 mg/m<sup>3</sup> (Gamble et al. 1984b). The FVC was 4.83 L in the high-exposure group, and 5.11 L in the low-exposure group, and the difference was statistically significant (p=0.02). The workers were exposed for an average of 12.2 years. No other significant changes in lung function tests (FEV<sub>1</sub>, peak flow) were noted. Effects on FEV<sub>1</sub> were not observed in workers exposed to acid aerosols (hydrochloric acid, 2.1 mg/m<sup>3</sup>; sulfuric acid, 0.5 mg/m<sup>3</sup>) for a maximum of 4.5 years (n=119-180) (Kremer et al. 1994), or to sulfuric acid aerosols (12.6-35 mg/m<sup>3</sup>) for from 1 to >15 years (n=20-33) (El-Sadik et al. 1972). For presentation in the Table 2-1 and Figure 2-1 only the low end of the concentration range is shown for the El-Sadik et al. (1972) study.

Among the animal species studied, guinea pigs are most sensitive to sulfuric acid aerosol exposure. During 1-hour nose-only exposures to 52-61 mg/m<sup>3</sup> sulfuric acid aerosols in the size range of 0.8-1.2 μm (MMAD), guinea pigs developed labored breathing and about 6% of the animals died (total number exposed was not stated) (Stengel et al. 1993). Excised lung gas volume (an indicator of in vivo airway obstruction and hyper-responsiveness) was increased in guinea pigs killed directly after the exposure but not 24 or 72 hours later. Labored breathing and hyperinflated lungs (resulting from reflex bronchoconstriction) were reported in guinea pigs (8 male, 8 female) exposed to sulfuric acid aerosols for 8 hours (Wolff et al. 1979). The effects were observed at 17.4 mg/m<sup>3</sup> for aerosols with an MMAD of 0.8 μm, and at 37.2 mg/m<sup>3</sup> for aerosols with an MMAD of 0.4 μm. Hemorrhage and transudation of the lungs were also observed following exposure to the large, but not the small, aerosol size.

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Dyspnea and cyanosis were observed in 20 guinea pigs within 10-30 minutes of a 4 hour exposure to 32.6 mg/m<sup>3</sup> sulfuric acid aerosol (MMAD 1.0 $\mu$ , RH 70-90%), but were not observed 24 hours following exposure (Brownstein et al. 1980). Lungs of guinea pigs sacrificed immediately after exposure contained areas which were hyperinflated and other areas which were collapsed. Interstitial edema was noted in the hyperinflated areas and alveolar edema was observed in the collapsed regions. Desquamation was observed primarily in the terminal bronchioles of collapsed regions. In Pungs of guinea pigs killed 24 hours after exposure, hyperinflated areas were less pronounced but collapsed regions were more defined. Also noted were infiltration of leukocytes in alveolar sacs and septums and fibrin deposits in areas where desquamation occurred.

The effect of aerosol size on lung function was studied in guinea pigs (n=5-11) exposed head-only to sulfuric acid while the animals were in a body plethysmograph (Amdur 1958). Control measurements for each guinea pig were completed during the 30 minutes before the 1 -hour exposure. In guinea pigs exposed to an aerosol size of 0.8  $\mu$ m (MMD), resistance increased about 1.5-fold at 1.9 mg/m<sup>3</sup>, and about 2.2-fold at 42 mg/ m<sup>3</sup>. Exposure to 2.5 $\mu$ m aerosols resulted in resistance increases of about 1.4-fold at 2.3 mg/ m<sup>3</sup> and 4.2-fold at 43.6 mg/m<sup>3</sup>. Increased lung weights and edema were also observed at the high concentration of 2.5- $\mu$ m aerosols. Resistance was increased about 1.4-fold in guinea pigs exposed to 30.5 mg/ m<sup>3</sup> sulfuric acid aerosols with an aerosol size of 7  $\mu$ m. In a comparison of the toxicity of the two smaller aerosol sizes, Amdur (1959) indicated that at higher concentrations the larger aerosols produced a greater response, while at the lower concentrations the smaller aerosols produced the greater response. The time course of the response to the two particle sizes was also different. The response to the smaller aerosol began at once, and after 10-15 minutes of exposure reached the final degree of response present at the end of the hour. Following exposure to the larger aerosol, there was little initial response; the effect occurred during the last 15-20 minutes of the exposure. Amdur (1958, 1959) suggested different mechanisms of response for the different aerosol sizes. The small aerosol (0.8  $\mu$ m) which would reach the more peripheral regions of the lungs may result in simple bronchoconstriction. The 2.5- $\mu$ m aerosols would have their major action on the main bronchi and may have resulted in local irritation of the larger air passages causing mucosal swelling, increased secretion, and possibly exudation of fluid leading to complete obstruction of major air passages. The larger aerosols (7  $\mu$ m) had little effect because they would not be expected to penetrate beyond the upper respiratory tract.

In an additional study of the effect of aerosol size on the response to sulfuric acid aerosols, Amdur et al. (1978) exposed 20-25 guinea pigs head-only to sulfuric acid aerosols with MMDs of 0.3 or 1  $\mu$ m.

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Pulmonary function measurements completed before and during the 1-hour exposures included pulmonary flow resistance, pulmonary compliance, tidal volume, respiratory frequency, and minute volume. No changes in tidal volume, respiratory frequency, or minute volume were noted. Pulmonary resistance was significantly increased by all exposures, with the smaller particles producing a greater response. For the 0.3- $\mu\text{m}$  aerosols, resistance was increased 41%, 60%, and 78% at 0.1, 0.51, and 1  $\text{mg}/\text{m}^3$ , respectively. For the 1- $\mu\text{m}$  aerosols, resistance was increased 14%, 30%, 47%, and 60% at 0.11, 0.4, 0.69, and 0.85  $\text{mg}/\text{m}^3$ , respectively. The resistance returned to control levels by the end of the 0.5-hour post-exposure period only at the lowest concentration of 1  $\mu\text{m}$ . Compliance was significantly decreased at all concentrations during exposure to 0.3- $\mu\text{m}$  aerosols (-27%, -33%, -40% at 0.1, 0.51 and 1  $\text{mg}/\text{m}^3$ , respectively), and at the two highest concentrations during exposure to 1  $\mu\text{m}$  aerosols (-25% and -28% at 0.69 and 0.85  $\text{mg}/\text{m}^3$ , respectively).

No effect on  $\text{SR}_{\text{aw}}$  was observed in 18 guinea pigs exposed to 3.2  $\text{mg}/\text{m}^3$  sulfuric acid aerosols (MMAD 0.5  $\mu\text{m}$ ) continuously for 3, 7, 14, or 30 days (Kobayashi and Shinozaki 1993). Transient changes in airway responsiveness to inhaled histamine were observed. After 3 days of exposure, a significant decrease in airway responsiveness was noted. An increase in responsiveness was noted after 14 days of exposure. The response to histamine was normal after 7 and 30 days of exposure. Increased airway responsiveness to acetylcholine was observed in 6-9 guinea pigs exposed head-only to sulfuric acid aerosols (MMD 0.06  $\mu\text{m}$ ) at 0.2  $\text{mg}/\text{m}^3$  for 1 hour (Chen et al. 1992b). No effects were observed at 0.03  $\text{mg}/\text{m}^3$ . Increased responsiveness to acetylcholine and histamine *in vitro* was observed in bronchial rings taken from 5 rabbits exposed nose-only to 0.075  $\text{mg}/\text{m}^3$  sulfuric acid (MMD 0.3  $\mu\text{m}$ ) for 3 hours (El-Fawal and Schlesinger 1994). No effects were observed at 0.05  $\text{mg}/\text{m}^3$ .

Bronchoprovocation challenge with intravenous acetylcholine was studied in 4-12 rabbits exposed nose-only to 0 or 0.25  $\text{mg}/\text{m}^3$  sulfuric acid aerosols (MMD 0.3  $\mu\text{m}$ ) 1 hour per day, 5 days per week, for 4, 8, or 12 months (Gearhart and Schlesinger 1986). Sulfuric acid exposure resulted in increased bronchial sensitivity at all exposure durations. The doses of acetylcholine that resulted in an increase in pulmonary resistance 150% of baseline ( $\text{ED}_{150\%}$ ) in  $\mu\text{g}/\text{kg}/\text{minute}$  were 0, 18.7, 2, 1.5, and 1.2 at 0, 2, 4, 8, and 12 months of exposure, respectively. Values at all time points were significantly different from the controls but not from each other. Exposure to sulfuric acid had no effects on dynamic compliance or respiratory rate. The study authors suggest that the lack of effect on dynamic compliance suggests that the site of increased airway responsiveness induced by sulfuric acid may have been predominantly the larger bronchi.

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A significant ( $p=0.01$ ) decrease in carbon monoxide diffusion capacity was observed in 4 beagle dogs exposed to  $0.755 \text{ mg/m}^3$  sulfuric acid (90% of the particles were  $<0.5 \text{ }\mu\text{m}$  in diameter) 21 hours per day for 225 days (Lewis et al. 1969). The diffusion capacity was  $6.3 \text{ mL/mmHg/min}$  in exposed dogs and  $7.4 \text{ mL/mmHg/min}$  in control dogs. Residual volume was  $163\pm 11 \text{ mL}$  and  $182\pm 12 \text{ mL}$  in control and exposed dogs, respectively. A statistical test for residual volume was not provided.

Clearance of particles has also been studied in animals. Clearance of  $^{51}\text{Cr}$ -chromium-labeled microspheres (activity median aerodynamic diameter [AMAD]  $1.9 \text{ }\mu\text{m}$ ) from the head was not affected in 10 ferrets exposed nose-only to  $0.5$  or  $1 \text{ mg/m}^3$  sulfuric acid aerosols (MMAD  $0.3 \text{ }\mu\text{m}$ ) for 4 hours (Mannix et al. 1991). Clearance from the lungs was significantly accelerated. The half-time of clearance was 1,126 hours in air-exposed ferrets, 773 hours at  $0.5 \text{ mg/m}^3$ , and 630 hours at  $1 \text{ mg/m}^3$ . Decreased clearance of  $^{85}\text{Sr}$ -strontium-labeled latex microspheres (MMAD  $3.5 \text{ }\mu\text{m}$ ) from the respiratory region of the lungs was observed in 3 rabbits exposed to  $0.05 \text{ mg/m}^3$  sulfuric acid aerosols (MMAD  $0.3 \text{ }\mu\text{m}$ ) 4 hours per day for 14 days (Schlesinger 1990a). Increased alveolar clearance of  $3.5\text{-}\mu\text{m}$  latex particles was observed in 4 rabbits exposed to sulfuric acid aerosols (MMD  $0.3 \text{ }\mu\text{m}$ ) at  $0.25 \text{ mg/m}^3$  for 1 hour per day, 5 days per week, for 1, 57, or 240 days (Schlesinger and Gearhart 1986).

The mucociliary clearance of  $^{99\text{m}}\text{Tc}$ -technetium-labeled ferric oxide particles (MMAD  $4.5 \text{ }\mu\text{m}$ ) was studied in groups of 8 rabbits exposed to sulfuric acid aerosols (MMAD  $0.3 \text{ }\mu\text{m}$ ) for 1 hour via an oral delivery tube. A concentration range of  $0.1\text{-}1.084 \text{ mg/m}^3$  was studied by Schlesinger et al. (1984), and a concentration range of  $0.260\text{-}2.155 \text{ mg/m}^3$  was studied by Chen and Schlesinger (1983). In these studies each rabbit was exposed multiple times. A series of 10 air-sham exposures was completed before any sulfuric acid aerosol exposures. Tests at each concentration were completed twice for each rabbit, and the order of exposure was randomized. The results of both studies, in terms of mean residence times, were presented in the Schlesinger et al. (1984) report. The complete data set was subjected to polynomial regression analysis, and the threshold concentration for no effects on clearance was  $0.1 \text{ mg/m}^3$ . At  $0.2 \text{ mg/m}^3$ , clearance was significantly increased, while at  $1.5 \text{ mg/m}^3$  clearance was significantly decreased. The study authors suggested that the increase in clearance at low concentrations and the decrease at higher concentrations may be a result of differential effects on the upper and lower bronchial tree. At low concentrations, sulfuric acid can stimulate mucus transport in the proximal airways of the bronchial tree where only small amounts of the aerosol are deposited, while it may slow transport in more distal airways.

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The effect of sulfuric acid exposure on particle clearance has been studied in donkeys and rabbits following intermediate or chronic exposure. For mucociliary clearance, donkeys are considered to closely model humans. A trend toward erratic and slower bronchial clearance of  $^{99m}$  technetium-tagged ferric oxide particles (MMAD 5  $\mu\text{m}$ ) was observed in 4 donkeys exposed nose-only to about 0.1 mg/ m<sup>3</sup> sulfuric acid aerosols (MMAD 0.5  $\mu\text{m}$ ) 1 hour per day, 5 days per week, for 6 months (Schlesinger et al. 1979). Each of the donkeys studied served as its own control. The effects on clearance were more prominent in 2 of the donkeys that had been used in a previous study involving twelve 1-hour sulfuric acid exposures. There was no evidence for persistence of effects from the earlier study. Effects on clearance of  $^{99m}$  technetium-tagged ferric oxide particles (MMAD 4.5  $\mu\text{m}$ ) were not observed during the exposure period in 5 rabbits exposed to 0.125 mg/ m<sup>3</sup> sulfuric acid (MMD 0.3  $\mu\text{m}$ ) 2 hours per day, 5 days per week, for 4, 8, or 12 months (Schlesinger et al. 1992a). During a 6-month recovery period, decreased clearance was observed in rabbits exposed for 12 months.

In rabbits (4/group) exposed to 0.25 mg/ m<sup>3</sup> sulfuric acid (MMD 0.3  $\mu\text{m}$ ) 1 hour/day, 5 days/week for 4, 8, or 12 months, a decrease in the clearance rate of  $^{99m}$  technetium-tagged ferric oxide particles was observed one week into the exposure period (Gearhart and Schlesinger 1989). The clearance rate continued to decrease throughout the exposure period and during a 3-month recovery period following the 12-month exposure time. Additional observations included progressive increases in the ratio of small to large airways, the number of secretory cells, and the acid glycoprotein content of mucous. During the 3-month recovery period, the numbers of secretory cells and the acid glycoprotein content of the mucous remained high, but the ratio of small to large airways no longer differed significantly from those of controls. The study demonstrated the persistence of certain sulfuric acid-induced effects up to three months past exposure.

The effects of sulfuric acid exposure on tracheal mucus were studied in rats and guinea pigs exposed in a chamber for 4 hours (Lee et al. 1995). Six rats were exposed to a concentration of 94.1 mg/ m<sup>3</sup> (MMD 0.8  $\mu\text{m}$ ), and 5 guinea pigs were exposed to a concentration of 43.3 mg/ m<sup>3</sup> (MMD 0.93  $\mu\text{m}$ ). Surface tension of the mucus was not affected by sulfuric acid exposure in either species, but electron microscopy indicated that the mucus layer was five or more times thicker in both species following sulfuric acid exposure, with a greater effect observed in guinea pigs. In water-exposed control guinea pigs the mucus layer was about 1  $\mu\text{m}$ , while it was 5-40  $\mu\text{m}$  in acid-exposed guinea pigs. The mucus of both species contained granular material and membrane-bound vesicles. Despite the changes in mucus, the acid aerosol exposure did not affect the ability of the mucus to submerge other particles. Some of the guinea pigs developed pulmonary edema, but further details were not provided.

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The effect of aerosol size on the levels of total protein, p-glucuronidase, and lactate dehydrogenase in lung lavage fluid has been studied in 6 guinea pigs exposed nose-only for 3 hours to filtered air or to 0.3 mg/m<sup>3</sup> sulfuric acid aerosols with an MMD of 0.3 or 0.04 μm (Chen et al. 1992a). The 3-hour exposure to the 0.3-μm aerosols resulted in increases in total protein, β-glucuronidase, and lactate dehydrogenase, while only P-glucuronidase was increased after exposure to the 0.04-μm aerosol. The increases were observed immediately after the exposure and were not observed 24 hours later. Lung lavage fluid levels of lactate dehydrogenase, prostaglandin E<sub>2</sub>, and prostaglandin F<sub>2α</sub> were not affected in 5 rabbits exposed to 0.125 mg/m<sup>3</sup> sulfuric acid aerosols (MMD 0.3 μm) for 3 hours (Schlesinger et al. 1992b). Lactate dehydrogenase in lung lavage fluid was also not affected in 5 rabbits exposed to 0.5 mg/m<sup>3</sup> sulfuric acid (MMD 0.3 μm) for 2 hours (Zelikoff and Schlesinger 1992). Lactate dehydrogenase and protein were increased in lung lavage fluid 24 hours after 5 rabbits were exposed to 1 mg/m<sup>3</sup> sulfuric acid aerosols (MMD 0.3 μm) 2 hours per day for 4 days (Zelikoff et al. 1994). No significant effects on the protein in the lung lavage fluid or on the lung tissue protein content were observed in 4-36 rats exposed to 1.29 mg/m<sup>3</sup> sulfuric acid aerosols (MMAD 0.4 μm) for 23.5 hours per day for 3 or 7 days (Warren and Last 1987). The collagen synthesis rate of the lungs was not affected in 12-41 rats exposed to 1.09 mg/m<sup>3</sup> sulfuric acid (MMAD 0.4 μm) 23.5 hours per day for 7 days (Warren and Last 1987).

Arachidonic acid metabolites (prostaglandins E<sub>2</sub> [PGE<sub>2</sub>] and F<sub>2α</sub> [PGF<sub>2α</sub>], thromboxane B<sub>2</sub> and leukotriene B<sub>4</sub>) were measured in the lung lavage fluid of 5 rabbits exposed to sulfuric acid (MMD 0.3 μm) 1 hour per day for 5 days at 0, 0.25, 0.5, or 1 mg/m<sup>3</sup> (Schlesinger et al. 1990b). Sulfuric acid exposure resulted in a reduction in PGE<sub>2</sub> production that was statistically significant beginning at 0.5 mg/m<sup>3</sup>, a reduction in PGF<sub>2α</sub> production that was statistically significant at 1 mg/m<sup>3</sup>, and a statistically significant reduction in thromboxane B<sub>2</sub> production at all exposure concentrations. No change in leukotriene B<sub>4</sub> production was observed. The significance of the effect of the reduction in these arachidonic acid metabolites that act as vasoconstrictors is not known.

In an 8-hour LC<sub>50</sub> study of groups of 5-12 guinea pigs exposed to 1-μm sulfuric acid aerosols in the range of 8-85 mg/m<sup>3</sup>, effects observed in the lungs of animals that survived for up to 3 weeks after the exposure included spotty areas of old hemorrhage and some areas of consolidation especially around the hilar regions (Amdur et al. 1952a). Adherence of the lungs to the diaphragm and pleural walls was sometimes observed. Microscopic pneumonic changes, fibrosis, thickening of the alveolar walls, atelectasis, and congestion of the alveolar space and bronchi were observed. The study authors indicated that the changes were consistent with a severe inflammatory process that had subsided. The concentrations at which the effects were observed were

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not stated. Microscopic lesions of the respiratory tract of the rats, mice, guinea pigs, and rabbits that died in the Treon et al. (1950) study were described as degenerative changes of the epithelium, pulmonary hyperemia and edema, some cases of focal pulmonary hemorrhages, and areas of atelectasis and emphysema. The microscopic changes were not described in relation to exposure concentration.

Diffuse regional alveolitis and varying degrees of septal edema were observed in 20 guinea pigs exposed to 10 mg/ m<sup>3</sup> sulfuric acid aerosols (MMD 0.89 μm) for 5, 7, 14, 21, or 28 days (Cavender et al. 1977). Microscopic examination of the lungs did not reveal any effects in 20 rats exposed to 100 mg/ m<sup>3</sup> sulfuric acid for 5 days (Cavender et al. 1977). The number of hours the guinea pigs and rats were exposed each day was not stated. Edema and hemorrhage were observed in the lungs of 10 male and 10 female guinea pigs exposed to 25 mg/ m<sup>3</sup> sulfuric acid aerosols (MMD 1 μm) 6 hours per day for 2 days (Cockrell et al. 1978). Transmission electron microscopy showed an increased number of type II alveolar cells; alveolar macrophages in the alveoli, and vacuoles were observed in type I cells. Lesions were not observed in the more proximal segments of the airways including the bronchi, trachea, or larynx.

Gross and microscopic examination of the nasal turbinates, trachea, and lungs of 35 mice exposed to 20 mg/m<sup>3</sup> sulfuric acid aerosols (CMD 2.4 μm) 7 hours per day on gestation days 6-15 revealed no evidence of toxicity that could be attributed to the exposure (Murray et al. 1979). Subacute rhinitis and tracheitis were observed in 20 rabbits exposed to 20 mg/m<sup>3</sup> sulfuric acid (CMD 2.4 μm) 7 hours per day on gestation days 6-18 (Murray et al. 1979).

The effect of aerosol size on pathological changes in the respiratory tract was studied in groups of 6-19 guinea pigs exposed to sulfuric acid aerosols for 32-139 days (Thomas et al. 1958). Exposure concentrations were 0.2, or 25 mg/ m<sup>3</sup> for the 0.5-μm aerosols, and 0 or 2-4 mg/ m<sup>3</sup> for the 0.9- and 4-μm aerosols. The guinea pigs, including controls, were sacrificed with chloroform, which may also have caused some lung effects. Microscopic examinations of pulmonary tissues were scored on a scale of 0-4, with 4 indicating the most severe effects. The alterations that were scored were atelectasis, emphysema, hyperemia, edema, hemorrhage, thrombosis of the alveolar capillaries, perivenous lymphocytic infiltration, distention of the lymph channels, extent and density of alveolar exudate, and the presence or absence of fibrosis. The medium aerosol size caused more effects in the lungs than the other sizes, while the large aerosol size caused greater effects in the upper respiratory tract. In the lungs, the average histological scores were 0.15, 0.63, and 0.28 for the small, medium, and large aerosols, respectively. In the upper respiratory

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tract, the average histological scores were 0.1, 0.04, and 0.76 for the small, medium, and large aerosols, respectively. The scores for individual histopathological changes never exceeded 2.

In a study using three aerosol sizes, histopathological changes in the respiratory tract were not observed in guinea pigs (50 male, 50 female) exposed to sulfuric acid 23 hours per day, 7 days per week, for 52 weeks (Alarie et al. 1973, 1975). No effects were observed at  $0.9 \text{ mg/m}^3$  at an MMD of  $0.49 \text{ }\mu\text{m}$ , at  $0.08 \text{ mg/m}^3$  at an MMD of  $0.84 \text{ }\mu\text{m}$ , or at  $0.1 \text{ mg/m}^3$  at an MMD of  $2.78 \text{ }\mu\text{m}$ . In cynomolgus monkeys (groups of 4-5 of each sex) exposed to sulfuric acid aerosols 23.3 hours per day, 7 days per week, for 78 weeks, histopathological changes were reported in the respiratory tract (Alarie et al. 1973). For the smaller aerosol size, moderate-to-severe bronchial epithelial hyperplasia and thickening of the walls of the respiratory bronchioles were observed in all 9 monkeys exposed at  $4.79 \text{ mg/m}^3$  (MMD  $0.73 \text{ }\mu\text{m}$ ), with no effects at  $0.48 \text{ mg/m}^3$  (MMD  $0.54 \text{ }\mu\text{m}$ ). In the monkeys exposed at  $4.79 \text{ mg/m}^3$ , no change in arterial oxygen was observed. For the larger aerosol size, moderate bronchiolar epithelial hyperplasia, thickening of the walls of the respiratory bronchioles, increases in the thickness of the alveolar walls, and hyperplasia and hypertrophy of the alveolar epithelial cells were observed in all 9 monkeys exposed to  $2.45 \text{ mg/m}^3$  (MMD  $3.6 \text{ }\mu\text{m}$ ). Because these effects were associated with decreased arterial oxygen (from 102 mmHg before exposure to 70 mmHg at 77 weeks) and a blood pH of 7.26-7.30, the  $2.45\text{-mg/m}^3$  concentration is considered a serious LOAEL. At a concentration of  $0.38 \text{ mg/m}^3$  (MMD  $2.15 \text{ }\mu\text{m}$ ), slight bronchiolar epithelial hyperplasia was observed in 5 of 9 monkeys, and slight thickening of the walls of the respiratory bronchioles was observed in 3 of 9 monkeys. No effects on alveoli or on arterial oxygen were observed at  $0.38 \text{ mg/m}^3$ .

**Cardiovascular Effects.** An electrocardiogram revealed abnormal ventricular activity in a previously healthy 40-year old male worker 7 months after he was accidentally sprayed in the face with 35% fuming sulfuric acid (equivalent to 108.04% sulfuric acid) and was exposed to sulfuric acid mists and vapors for 8 minutes while he rinsed himself off in a safety shower (Goldman and Hill 1953). The subject suffered permanent pulmonary damage which eventually led to the development of fibrosis and emphysema, but there was no discussion as to whether the cardiac effect was secondary to pulmonary injury. Heart rate at the time of transition between nasal and oronasal breathing was not affected in 7 exercising healthy human subjects exposed head-only to  $0.471 \text{ mg/m}^3$  sulfuric acid aerosols (MMAD  $10 \text{ }\mu\text{m}$ ) for 1 hour (Bowes et al. 1995). An association between ambient sulfate concentrations and myocardial infarctions was observed among 6,340 nonsmokers in California only with exceedance frequencies greater than  $6 \text{ }\mu\text{g/m}^3$  of sulfate (Abbey et al. 1995). Interpretation of air pollution studies requires caution because it is difficult to separate effects associated with individual air pollutants.

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Histopathological changes in the heart were not observed in 9 cynomolgus monkeys exposed to sulfuric acid aerosols at up to 4.79 mg/ m<sup>3</sup>, 23.3 hours per day, 7 days per week, for 78 weeks (Alarie et al. 1973), or in guinea pigs (groups of 50 of each sex) at concentrations up to 0.9 mg/ m<sup>3</sup>, 23 hours per day, 5 days per week, for 52 weeks (Alarie et al. 1973, 1975).

**Hematological Effects.** Red blood cell glutathione reductase level was unaffected in 18 healthy males exposed to 0.1 mg/m<sup>3</sup> sulfuric acid (MMD 0.5 μm) for 4 hours (Chaney et al. 1980).

Changes in hematocrit, hemoglobin, red blood cell counts, and white blood cell counts were not observed in 9 cynomolgus monkeys exposed to sulfuric acid aerosols at up to 4.79 mg/m<sup>3</sup>, 23.3 hours per day, 7 days per week, for 78 weeks (Alarie et al. 1973), or in guinea pigs at concentrations up to 0.9 mg/m<sup>3</sup>, 23 hours per day, 5 days per week, for 52 weeks (Alarie et al. 1973, 1975).

**Hepatic Effects.** Biochemical blood parameters, such as serum glutathione, 2,3-diphosphoglycerate, serum glutamic oxaloacetic acid transaminase, and serum vitamin E were unaffected in 18 healthy males exposed to 0.1 mg/ m<sup>3</sup> sulfuric acid (MMD 0.5 μm) for 4 hours (Chaney et al. 1980).

No effects on liver weight were noted in mice or rabbits exposed to 20 mg/ m<sup>3</sup> sulfuric acid aerosols (CMD 2.4 μm) 7 hours per day on gestation days 6-15 for 35 mice and days 6-18 for 20 rabbits (Murray et al. 1979). Microscopic changes in the liver and treatment-related changes in serum levels of liver enzymes were not observed in cynomolgus monkeys exposed to sulfuric acid aerosols at up to 4.79 mg/ m<sup>3</sup>, 23.3 hours per day, 7 days per week, for 78 weeks (Alarie et al. 1973), or in guinea pigs at concentrations up to 0.9 mg/ m<sup>3</sup>, 23 hours per day, 5 days per week, for 52 weeks (Alarie et al. 1973, 1975). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in both species; lactic acid dehydrogenase and alkaline phosphatase were also measured in monkeys. The liver enzyme data were not presented in the paper. However, the authors stated that enzyme levels were highly variable in all groups of monkeys and there were no trends suggesting effects related to exposure.

**Renal Effects.** No studies were located regarding renal effects in humans after inhalation exposure to sulfur trioxide or sulfuric acid.

Treatment-related microscopic changes in the kidneys were not observed in 9 cynomolgus monkeys (Alarie et al. 1973) or in guinea pigs (50 of each sex) (Alarie et al. 1973, 1975) exposed chronically to sulfuric acid

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aerosols. The monkeys were exposed to sulfuric acid aerosols at up to 4.79 mg/ m<sup>3</sup> 23.3 hours per day, 7 days per week, for 78 weeks (Alarie et al. 1973). The guinea pigs were exposed at concentrations up to 0.9 mg/ m<sup>3</sup> 23 hours per day, 5 days per week, for 52 weeks (Alarie et al. 1973, 1975).

**Dermal Effects.** No studies were located regarding dermal effects in humans or animals after inhalation exposure to sulfur trioxide or sulfuric acid.

**Ocular Effects.** Lacrimation was reported in volunteers exposed to sulfuric acid aerosols (MMD 1.54 μm) at 20.8 mg/ m<sup>3</sup> (Sim and Pattle 1957). The exposures, completed at a relative humidity of 91%, were almost intolerable at the onset. Eye irritation was not reported by subjects exposed to a concentration of 39.4 mg/ m<sup>3</sup> (MMD 0.99 μm) at a relative humidity of 63%. This study is of limited value because the subjects were allowed to smoke during the exposures. Minor eye irritation was significantly increased in asthmatics exposed to 0.999 and 1,460 mg/ m<sup>3</sup> sulfuric acid mist (MMD 0.9 μm) for 1 hour (Avol et al. 1988). However, statistically significant increases in eye irritation were not reported by healthy subjects exposed to concentrations as high as 1,578 mg/ m<sup>3</sup> under the same conditions.

No studies were located regarding ocular effects in animals after inhalation exposure to sulfur trioxide or sulfuric acid.

**Body Weight Effects.** No effects on body weight gain were noted in mice or rabbits exposed to 20 mg/ m<sup>3</sup> sulfuric acid aerosols (CMD 2.4 μm) 7 hours per day on gestation days 6-15 for mice and days 6-18 for rabbits (Murray et al. 1979). Effects on body weight were not observed in rabbits exposed to 0.125 mg/ m<sup>3</sup> sulfuric acid aerosols (MMD 0.3 μm) 2 hours per day, 5 days per week, for 4, 8, or 12 months (Schlesinger et al. 1992a). Chronic exposure to sulfuric acid aerosols also had no effect on body weights of cynomolgus monkeys (Alarie et al. 1973) or guinea pigs (Alarie et al. 1973, 1975). The monkeys were exposed to sulfuric acid aerosols at up to 4.79 mg/ m<sup>3</sup> 23.3 hours per day, 7 days per week, for 78 weeks (Alarie et al. 1973). The guinea pigs were exposed at concentrations up to 0.9 mg/ m<sup>3</sup> 23 hours per day, 5 days per week, for 52 weeks (Alarie et al. 1973, 1975).

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**Other Systemic Effects.** Studies of workers indicate that exposure to sulfuric acid aerosols can result in lowered pH of the saliva (El-Sadik et al. 1972), erosion of the teeth (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961), and increased prevalence of periodontal pockets (Tuominen 1991). The subjects in the El-Sadik et al. (1972) study were exposed to concentrations of 12.6-35 mg/ m<sup>3</sup>. Only the low end of the concentration range is shown in Table 2- 1 and Figure 2- 1. The lowest average concentration at which effects on the teeth were noted was 0.21 mg/ m<sup>3</sup> for 248 workers exposed an average of 12.2 years (Gamble et al. 1984a). Malcolm and Paul (1961) indicated that the front teeth of the 63 exposed workers in their study were the teeth most often affected, suggesting the effect was the result of direct impingement of acid mist on the teeth.

No studies were located regarding other systemic effects in animals after inhalation exposure to sulfur trioxide or sulfuric acid.

### 2.2.1.3 Immunological and Lymphoreticular Effects

The function of alveolar macrophages was studied in cells collected by lung lavage 18 hours after 12 volunteers were exposed to 1 mg/ m<sup>3</sup> sulfuric acid and sodium chloride aerosol (MMAD 0.9 μm) for 2 hours each (Frampton et al. 1992). The sulfuric acid and sodium chloride exposures were separated by at least 2 weeks. Sulfuric acid exposure had no effect on cell recovery in the lavage fluid, providing no evidence of an inflammatory response. The ability of alveolar macrophages to lyse antibody-coated red blood cells showed a small increase following sulfuric acid exposure. This effect was not considered to be adverse. The ability of alveolar macrophages to become associated with and inactivate influenza virus was not significantly affected by sulfuric acid exposure.

Increased mortality was not observed in 80 mice challenged for 20 minutes with an aerosol of *Streptococcus pyogenes* directly after head-only exposures to ultrafine (VMD <0.1 μm) sulfuric acid aerosols (Grose et al. 1982). The mice were exposed to sulfuric acid for 2 hours at 0.543 mg/ m<sup>3</sup> or for 2 hours per day for 5 days at 0.365 mg/ m<sup>3</sup>.

Additional animal studies have examined the *in vitro* function of immune cells collected by lung lavage from animals exposed to sulfuric acid aerosols. Intracellular pH of alveolar macrophages was decreased in guinea pigs 15.6% following a single 3-hour chamber exposure and by 23.5% after five 3-hour exposures to 0.97 mg/ m<sup>3</sup> sulfuric acid (MMD 0.3 μm) (Qu et al. 1993). Decreased intracellular pH of alveolar

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macrophages was also observed in macrophages from rabbits exposed nose-only to 0.125 mg/ m<sup>3</sup> sulfuric acid aerosols (MMD 0.3 μm) for 3 hours (Chen et al. 1995). No effect was observed at 0.05 mg/ m<sup>3</sup>. Intracellular pH must be maintained within a narrow range to ensure normal cell functions such as regulation of the cell cycle and signal transduction (Chen et al. 1995; Qu et al. 1993).

A single 3-hour exposure of guinea pigs to 0.3 mg/ m<sup>3</sup> sulfuric acid aerosol with an MMD of 0.3 μm enhanced the phagocytic activity of alveolar macrophages 24 hours after exposure (Chen et al. 1992a). A single 3-hour exposure to 0.3 mg/ m<sup>3</sup> sulfuric acid aerosol with an MMD of 0.04 μm depressed the ability of alveolar macrophages to phagocytize particles. The study authors suggested that, compared to larger droplets, smaller droplets deliver a higher dose to the alveolar macrophages. Endotoxin-stimulated production of tumor necrosis factor (TNF) by alveolar macrophages was significantly increased by four daily 3-hour exposures to 0.3 mg/ m<sup>3</sup> sulfuric acid at MMDs of both 0.04 and 0.3 μm (Chen et al. 1992a).

A series of studies has been completed in which macrophage function has been studied in rabbits following exposure to sulfuric acid aerosols with an MMD of 0.3 μm (Schlesinger 1987; Schlesinger et al. 1990a, 1992b; Zelikoff and Schlesinger 1992; Zelikoff et al. 1994). A 2-hour exposure to 0,0.05,0.075,0.125, or 0.5 mg/ m<sup>3</sup> sulfuric acid aerosols had no effect on the number of cells recovered in lavage fluid, the percentage of polymorphonuclear cells, or macrophage viability (Zelikoff and Schlesinger 1992). At the three highest concentrations, sulfuric acid exposure significantly reduced macrophage TNF cytotoxic activity directed towards a tumorigenic target cell and reduced zymosan-stimulated production of superoxide anion. The effects at the three highest concentrations were not significantly different from each other. Following a 3-hour exposure to 0.075 mg/ m<sup>3</sup>, decreased phagocytic activity, production of superoxide anion, and TNF activity were observed, with no effects at 0.05 mg/ m<sup>3</sup> (Schlesinger et al. 1992b). Macrophage-mediated immunity was suppressed following 4 daily 2-hour exposures to 0.75 mg/ m<sup>3</sup> (Zelikoff et al. 1994), 5 daily 1-hour exposures to 1 mg/ m<sup>3</sup> (Schlesinger et al. 1990a), and 13 daily 2-hour exposures to 0.5 mg/ m<sup>3</sup> (Schlesinger 1987). Based on the results of their studies of macrophage function, Zelikoff et al. (1994) concluded that there was an absence of a concentration-response relationship. Once a critical level of acid was reached, no further effects were observed.

The release of histamine from antigen- or A23 187-induced mast cells was studied in cells collected from guinea pigs exposed continuously to 0,0.3, 1, or 3.2 mg/ m<sup>3</sup> sulfuric acid aerosols with MMDs in the range of 0.55-0.73 μm for 2 or 4 weeks (Fujimaki et al. 1992). Sulfuric acid exposure did not have any effects on the number of mast cells in the lavage fluid. Antigen-induced histamine release from mast cells was significantly

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enhanced at 1 and 3.2 mg/m<sup>3</sup> following 2 weeks of exposure, but not after 4 weeks of exposure. A23187-induced histamine release was enhanced at 1 mg/m<sup>3</sup> following 2 weeks of exposure but was suppressed at 3.2 mg/m<sup>3</sup> following 4 weeks of exposure. No effects on mast cell function were noted at 0.3 mg/m<sup>3</sup>.

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

**2.2.1.4 Neurological Effects**

Lightheadedness and dizziness were reported by 3 of 12 persons accidentally exposed to sulfur trioxide for approximately 2 hours (Stueven et al. 1993). The exposure concentrations were not stated.

Fatigue and headaches were reported more frequently in 21 asthmatic volunteers exposed to sulfuric acid aerosols at 0.999 mg/m<sup>3</sup> (MMD 0.9 μm) for 1 hour (Avol et al. 1988). These subjective symptoms were not reported at 0.396 mg/m<sup>3</sup>, nor were they reported by 21 normal volunteers exposed to sulfuric acid aerosol concentrations as high as 1.578 mg/m<sup>3</sup>.

Uncoordinated movements were observed in three guinea pigs following a 15minute exposure to 165 mg/m<sup>3</sup> sulfuric acid mist (1-2 μm) but were not reported following exposure to higher doses (Treon et al. 1950).

The NOAELs and LOAEL for neurological effects in humans identified in the Avol et al. (1988) study are recorded in Table 2-1 and plotted in Figure 2-1a

**2.2.1.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans after inhalation exposure to sulfur trioxide or sulfuric acid.

No significant effects on the mean numbers of implants/dam or resorptions/litter were noted in 35 mice or 20 rabbits exposed to 20 mg/m<sup>3</sup> sulfuric acid aerosols (CMD 2.4 μm) 7 hours per day on gestation days 6-15 for mice and 6-18 for rabbits (Murray et al. 1979).

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The NOAEL values for mice and rabbits for reproductive effects are recorded in Table 2- 1 and plotted in Figure 2-1.

**2.2.1.6 Developmental Effects**

No studies were located regarding developmental effects in humans after inhalation exposure to sulfur trioxide or sulfuric acid.

No significant effects on fetal body weights or on the incidence of major or minor malformations were noted in the offspring of 35 mice or 20 rabbits exposed to 20 mg/ m<sup>3</sup> sulfuric acid aerosols (CMD 2.4 μm) 7 hours per day on gestation days 6-15 for mice and 6-18 for rabbits (Murray et al. 1979).

The NOAEL values for mice and rabbits for developmental effects are recorded in Table 2-1 and plotted in Figure 2- 1.

**2.2.1.7 Genotoxic Effects**

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to sulfur trioxide or sulfuric acid.

Genotoxicity studies are discussed in Section 2.5.

**2.2.1.8 Cancer**

In a study regarding the effect of air pollutants in nonsmokers, sulfates were not shown to be associated with cancer (Abbey et al. 1995). Increases in respiratory tract cancers were not observed among a cohort of 400 male workers at a sulfuric acid plant in Sweden (Englander et al. 1988). The men were exposed to sulfuric acid aerosols at concentrations of <0.1-2.9 mg/ m<sup>3</sup> for at least 6 months. There was a significant (p=0.006) increase in bladder cancer in this population. The study authors suggested that bladder cancer in this population may not be a result of sulfuric acid aerosol exposure but may have been a result of chance or smoking or other factors such as diet.

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A case of laryngeal cancer was reported in a man (life-long nonsmoker) exposed to sulfuric acid from poorly maintained batteries used to operate an electric forklift truck (Houghton and White 1994). The man operated a fork lift truck for 11 years. Exposure concentrations were not stated, but the man described the surface of the batteries as always being wet with sulfuric acid; he often suffered burns on his legs and clothing damage. Employment history did not reveal exposure to any other industrial carcinogens. Three cases of laryngeal cancer were reported among 78 workers at a factory that pickled stainless steel pipes (Ahlborg et al. 1981). Based on cancer registry data, 0.05 laryngeal cancer cases would have been expected in this population. All three persons with laryngeal cancer were moderate smokers. Exposures included sulfuric acid, nitric acid, oxalic acid, ammonium bifluoride, soap, sodium thiosulfate, sodium hydrosulfite, hydrogen fluoride, and low levels of chromium, nickel, and asbestos.

Occupational studies of isopropyl alcohol production workers (Alderson and Rattan 1980), soap production workers (Forastiere et al. 1987), and refinery and chemical plant workers (Soskolne et al. 1982, 1984, 1992) have reported small increases of upper respiratory tract cancers (nasal, laryngeal) and lung cancers in workers exposed to sulfuric acid aerosols. Exposure concentrations were not well characterized in these studies. In a study of workers from two battery manufacturers and two steel works in Britain, a small increase in upper respiratory tract cancers (e.g., lip, retromolar area, tongue, nasopharynx, tonsil, larynx, gum, and nasal sinus) was observed (Coggon et al. 1996). The study authors indicated that a small increase in risk occurred at  $1 \text{ mg/ m}^3$ , but not at lower concentrations. Although this study provides limited evidence that the risk of cancer in the upper respiratory and digestive system is increased, the risk estimate was based on a small number of cases, and the excess was not significant. The study does not provide any information on alcohol or tobacco use. There is also no information about exposure before 1970.

In a study of male steel workers exposed to acid mists during pickling operations at an average concentration of  $0.2 \text{ mg/ m}^3$  for an average of 9.5 years, a statistically significant increase in laryngeal cancer was observed (Steenland et al. 1988). Nine of 879 workers were diagnosed with laryngeal cancer, while after adjusting for smoking, 3.44 cases of laryngeal cancer were expected. All cases were either current or former smokers. Quantitative individual sulfuric acid exposure data were not provided. The study authors indicated that the pickling process did not generate appreciable levels of metal particulates. This population has also been studied for lung cancer (Beaumont et al. 1987; Steenland and Beaumont 1989). A total of 41 lung cancers in a cohort of 1,165 steelworkers were identified (Steenland and Beaumont 1989). The standardized mortality ratio (SMR) for lung cancer after adjusting for smoking for those with 20 years or more since first exposure was 1.5, with a 95% confidence interval of 1.05-2.27 (Steenland and Beaumont 1989). There was little

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evidence of a duration-response effect, and possible confounders such as exposure to nickel and silica were not considered in this study.

A case control study was conducted of 352 white males with laryngeal cancer and 1,050 white male controls admitted to a hospital between 1957 to 1965. Exposure to sulfuric acid was estimated through a review of occupational history. The risk of developing laryngeal cancer was significantly greater in heavy smokers with occupational exposures to sulfuric acid than in heavy smokers with no sulfuric acid exposure. Relative risks for laryngeal cancer were 2.43 and 2.05 in heavy smokers exposed to sulfuric acid for  $\geq 20$  years and heavy smokers exposed to sulfuric acid for  $< 20$  years, respectively (Cookfair et al. 1985). The study is limited because actual exposure concentrations were not known.

No studies were located regarding cancer in animals after inhalation exposure to sulfur trioxide or sulfuric acid.

### 2.2.2 Oral Exposure

No studies in humans or animals were located regarding oral exposure to sulfur trioxide.

#### 2.2.2.1 Death

Mineral acids, including sulfuric acid, are commonly used as cleaning agents in India. In a report of 10 human cases of sulfuric acid ingestion from January 1978 to December 1980, 2 died (Dilawari et al. 1984). One person died of gastric perforation, and the second person died of bronchopneumonia. Although the concentration of sulfuric acid ingested by these subjects was not stated, the concentration of sulfuric acid available in India is in the range of 26.4-35.4 Normal (N).

The  $LD_{50}$  in rats treated by gavage with reagent grade sulfuric acid in water at a concentration of 0.25 g/mL was reported as 2,140 mg/kg (Smyth et al. 1969). No deaths were reported in chicks fed sulfuric acid in the diet at 11,117 mg/kg/day for 14 days (Capdevielle and Scanes 1995b), or mallard ducklings fed sulfuric acid in the diet at 12,393 mg/kg/day for 15 days (Capdevielle and Scanes 1995a). These studies indicate that a much larger dose of sulfuric acid can be tolerated if it is given in the food compared to gavage treatment. When sulfuric acid is added to food, some will be neutralized.

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The LD<sub>50</sub> for rats is recorded in Table 2-2 and plotted in Figure 2-2.

**2.2.2.2 Systemic Effects**

No studies were located regarding cardiovascular, hematological, dermal, or ocular effects in humans or animals after oral exposure to sulfuric acid.

**Respiratory Effects.** In a report of 10 humans who ingested sulfuric acid, 2 died (Dilawari et al. 1984). One person died of bronchopneumonia. The amount of sulfuric acid ingested by this subject was not provided.

No studies were located regarding respiratory effects in animals after oral exposure to sulfuric acid.

**Gastrointestinal Effects.** A 2-year-old boy who ingested an unspecified amount of sulfuric acid required surgery to replace his stomach with a jejunal pouch (Aktug et al. 1995). In a report from India regarding 10 humans who ingested sulfuric acid, 2 died (Dilawari et al. 1984). The cause of death was gastric perforation in 1 person. Endoscopy was completed in ah 10 subjects and the gastrointestinal lesions were graded as follows: I) mild mucosal hyperaemia; II) moderate superficial ulcerations; and IU) severe, extensive, deep ulcerations. Among the survivors, there were 4 cases each with esophageal lesions of grade II and grade III. Stomach lesions of grade III were observed in 6 survivors, and grade II in 2 survivors. Grade III lesions were observed only in the duodenum of the 2 subjects who died. Duodenal lesions were grade I in 3 survivors, with no duodenal lesions observed in the other 5 survivors. The amount and concentration of the acid consumed by the individuals were not known, but the study authors estimated that the amount was in the range of 15-50 mL, and the concentration was up to 26.4-35.4 N, which is the concentration of acid readily available in India.

No studies were located regarding gastrointestinal effects in animals after oral exposure to sulfuric acid.

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans after oral exposure to sulfuric acid.

As an indication of growth, tibia length was measured in chicks (Capdevielle and Scanes 1995b) and mallard ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. Decreased tibia length, associated

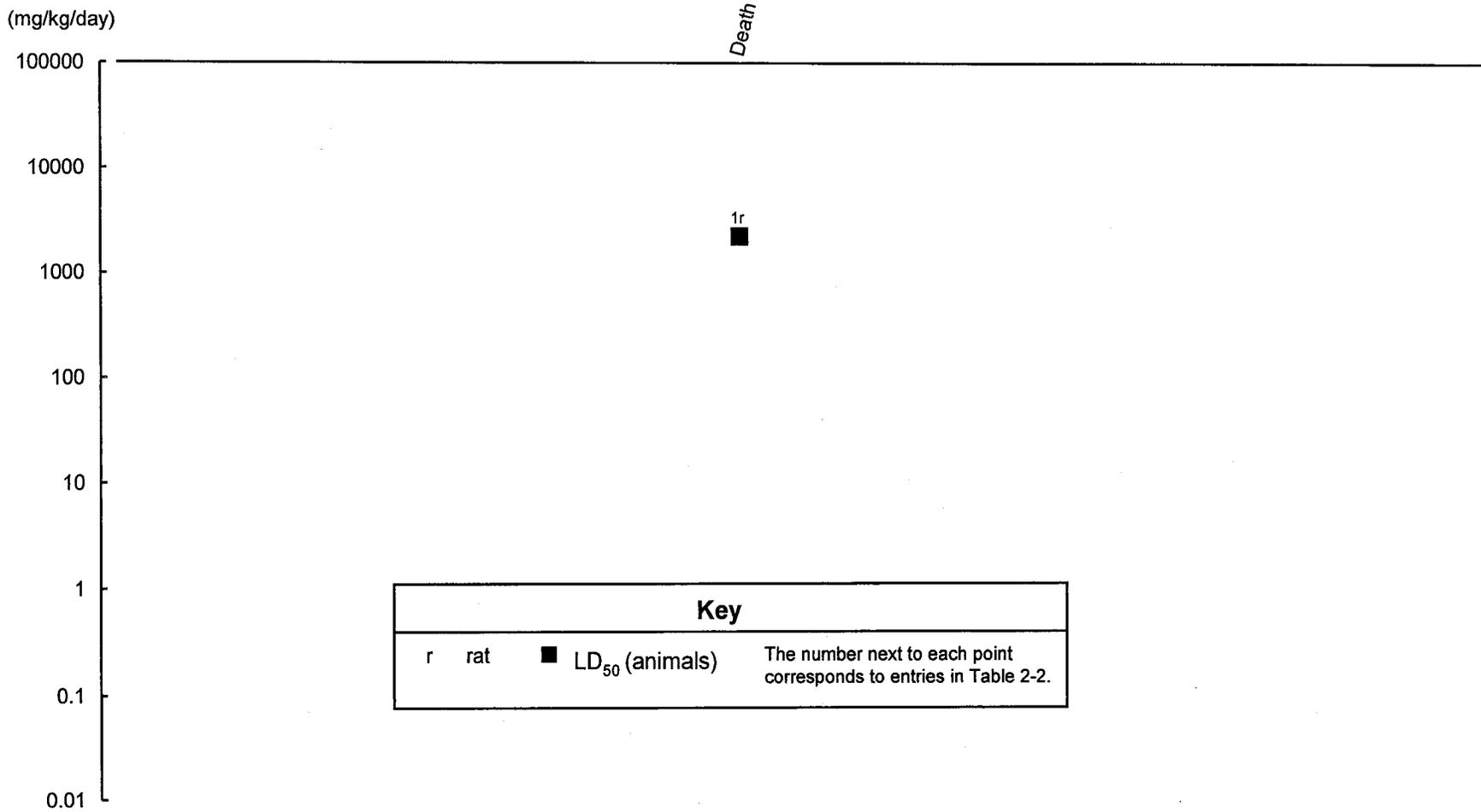
Table 2-2. Levels of Significant Exposure to Sulfuric Acid - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>							
<b>Death</b>							
1	Rat (NS)	once (GW)				2140 (LD <sub>50</sub> )	Smyth et al. 1969

<sup>a</sup>The numbers correspond to entries in Figure 2-2.

(GW) = gavage water; LD<sub>50</sub> = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; (NS) = not specified

**Figure 2-2. Levels of Significant Exposure to Sulfuric Acid - Oral**  
**Acute ( $\leq 14$  days)**



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with an 18% decrease in food intake, was observed in chicks fed 11,117 mg/kg/day for 14 days, with no effects at 2,338 mg/kg/day (Capdevielle and Scanes 1995b). No effect on tibia length or food intake was observed in mallard ducklings fed sulfuric acid at 12,393 mg/kg/day for 15 days (Capdevielle and Scanes 1995a). The study authors suggested that the difference between chickens and ducks may be a result of the eating habits of ducks. Ducks often dip toxicant-treated food into water before eating it, which may have diluted the acid, thus minimizing the effects on ducks

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

No changes in liver weight were observed in chicks fed 11,117 mg/kg/day of sulfuric acid in the diet for 14 days (Capdevielle and Scanes 1995b) or in mallard ducklings fed 12,393 mg/kg/day sulfuric acid in the diet for 15 days (Capdevielle and Scanes 1995a).

**Renal Effects.** No studies were located regarding renal effects in humans after oral exposure to sulfuric acid.

No changes in kidney weights were observed in chicks fed 11,117 mg/kg/day of sulfuric acid in the diet for 14 days (Capdevielle and Scanes 1995b) or in mallard ducklings fed 12,393 mg/kg/day of sulfuric acid in the diet for 15 days (Capdevielle and Scanes 1995a).

**Endocrine Effects.** No studies were located regarding endocrine effects in humans after oral exposure to sulfuric acid.

No changes in plasma growth hormone, insulin-like growth factor, and insulin-like growth factor binding proteins were observed in chicks fed 11,117 mg/kg/day of sulfuric acid in the diet for 14 days (Capdevielle and Scanes 1995b) or in mallard ducklings fed 12,393 mg/kg/day of sulfuric acid in the diet for 15 days (Capdevielle and Scanes 1995a). The lack of an endocrine effect suggests that the decreases in growth observed in chicks were a result of the decreased food intake.

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**Body Weight Effects.** Decreased body weight gain associated with an 18% decrease in food intake was observed in chicks fed 11,117 mg/kg/day sulfuric acid in the diet for 14 days, with no effects at 2,338 mg/kg/day (Capdevielle and Scanes 1995b). No effect on body weight gain or food intake was observed in mallard ducklings fed sulfuric acid in the diet at 12,393 mg/kg/day for 15 days (Capdevielle and Scanes 1995a). The study authors suggest that the difference between chickens and ducks may be a result of different eating habits of ducks. Ducks often dip toxicant-treated food into water before eating it, which may have diluted the acid, thus minimizing the effects on the ducks.

**2.2.2.3 Immunological and Lymphoreticular Effects**

No studies were located regarding immunological and lymphoreticular effects in humans or animals following oral exposure to sulfuric acid.

**2.2.2.4 Neurological Effects**

No studies were located regarding neurological effects in humans or animals following oral exposure to sulfuric acid.

**2.2.2.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans after oral exposure to sulfuric acid.

Changes in testes weights were not observed in chicks fed 11,117 mg/kg/day of sulfuric acid in the diet for 14 days (Capdevielle and Scanes 1995b) or in mallard ducklings fed 12,393 mg/kg/day of sulfuric acid in the diet for 15 days (Capdevielle and Scanes 1995a).

**2.2.2.6 Developmental Effects**

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

As indicated under musculoskeletal effects and body weight effects, decreased growth (decreased tibia length and decreased body weight gain) associated with an 18% decrease in food intake was observed in chicks fed 11,117 mg/kg/day sulfuric acid in the diet for 14 days, with no effects at 2,338 mg/kg/day (Capdevielle and

## 2. HEALTH EFFECTS

Scanes 1995b). This effect on growth was not accompanied by changes in plasma growth hormone, insulinlike growth factor, or insulin-like growth factor binding protein. No effect on growth or food intake was observed in mallard ducklings fed sulfuric acid in the diet at 12,393 mg/kg/day for 15 days (Capdevielle and Scanes 1995a). The study authors suggest that the difference between chickens and ducks may be a result of different eating habits of ducks. Ducks often dip toxicant-treated food into water before eating it, which may have diluted the acid, thus minimizing the effects on the ducks.

**2.2.2.7 Genotoxic Effects**

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

Genotoxicity studies are discussed in Section 2.5.

**2.2.2.8 Cancer**

No studies were located regarding cancer in humans or animals after oral exposure to sulfuric acid.

**2.2.3 Dermal Exposure**

No studies in humans or animals were located regarding dermal exposure to sulfur trioxide.

**2.2.3.1 Death**

Death can occur from dermal burns from chemicals including sulfuric acid. In a report of burns from chemicals that included sulfuric acid and that occurred in Jamaica as a result of assault, Branday et al. (1996) indicated that deaths occurred in people whose chemical burn injuries exceeded 50% of the total body surface area. The death of a man 5 days after he was deliberately splashed with a solution containing concentrated sulfuric acid (concentration not reported) was attributed to extensive burns and chemical damage to the respiratory tract (Schultz et al. 1968). The man was splashed over his face and body, and he received second-degree burns over 60% of his body and third-degree burns over 20% of his body.

No studies were located regarding deaths in animals after dermal exposure to sulfuric acid.

### 2.2.3.2 Systemic Effects

The highest NOAEL and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2-31

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or body weight effects in humans or animals after dermal exposure to sulfuric acid.

**Dermal Effects.** Direct application of concentrated sulfuric acid to the skin resulted in chemical burns in exposed humans (Branday et al. 1996; Schultz et al. 1968). The effects reported included coagulative necrosis and third-degree burns (Schultz et al. 1968). The concentration required to result in dermal burns in humans has not been determined. Dermal exposure of humans for 4 hours to a 10% sulfuric acid solution was considered nonirritating (Nixon et al. 1975). The sulfuric acid was applied to both intact and abraded skin on a 4-cm area on the back of each person. The sites were evaluated for erythema and edema on a scale of 0-4 at 4,24, and 48 hours after the application. Additional details about the methods were not provided by the study authors, although they indicate that the test was completed by a procedure proposed by the FDA in 1972. The mean score for humans was 0.2 for both intact and abraded skin.

Sulfuric acid placed directly on the skin is corrosive. Available animal studies do not agree on the concentration required to produce direct skin effects. Erosion of the skin at 10%, erythema and edema at 5%, and no effects at 2.5% were reported in rats and mice in which 1 mL/kg of the acid was placed on the electric razor-shaved skin of the back (Sekizawa et al. 1994). The application area was left unoccluded, and the animals wore collars and were caged separately to prevent licking. The skin was examined for 1 week after the application. In comparison to the Sekizawa et al. (1994) study, no skin effects were observed in guinea pigs or rabbits in which a 10% sulfuric acid solution was applied to the skin for 4 hours (Nixon et al. 1975). The sites were evaluated for erythema and edema on a scale of 0-4 at 4,24, and 48 hours after the application. Additional details about the methods were not provided by the study authors, although they indicate that the test was completed by a procedure proposed by the FDA in 1972. The mean score was 0 for both intact and abraded skin in guinea pigs and for intact skin in rabbits. The mean score was 0.1 for abraded skin in rabbits. During a 4-hour exposure, sulfuric acid was not corrosive to the skin when 0.5 mL of a 4% solution was placed on the backs of rabbits that were clipped of hair 24 hours before exposure (Vemot et al. 1977).

Table 2-3. Levels of Significant Exposure to Sulfuric Acid - Dermal<sup>a</sup>

Species (Strain)	Exposure/ Duration/ Frequency	System	NOAEL (percent)	LOAEL		Reference
				Less serious (percent)	Serious (percent)	
<b>ACUTE EXPOSURE</b>						
<b>Systemic</b>						
Human-a	1 hr (WB)	Ocular	0.396 <sup>b</sup> mg/m <sup>3</sup>	0.999 <sup>b</sup> mg/m <sup>3</sup>	(eye irritation)	Avol et al. 1988  MMD 0.9
Human	4 hr	Dermal	10			Nixon et al. 1975
Rat (Wistar)	once	Dermal	2.5 M	5 M (erythema, edema)		10 M (erosion of skin)  Sekizawa et al. 1994
Rat (Wistar)	once	Ocular	1-1.25 M	2.5 M (iris swelling, cornea diffuse)		Sekizawa et al. 1994
Mouse (ddY)	once	Dermal	2.5 M	5 M (erythema, edema)		10 M (erosion of skin)  Sekizawa et al. 1994
Mouse (ddY)	once	Ocular	1-1.25 M	2.5 M (iris swelling, cornea diffuse)		Sekizawa et al. 1994
Gn Pig (Hartley)	4 hr	Dermal	10			Nixon et al. 1975
Rabbit (New Zealand)	once	Ocular	10			Jacobs 1992
Rabbit (New Zealand)	once	Ocular		5 (minimal corneal opacities in 3/12)		10 (severe corneal opacities in 12/12)  Murphy et al. 1982

Table 2-3. Levels of Significant Exposure to Sulfuric Acid - Dermal (continued)

Species (Strain)	Exposure/ duration/ frequency	System	NOAEL (percent)	LOAEL		Reference
				Less serious (percent)	Serious (percent)	
Rabbit (NS)	4 hr	Dermal	10			Nixon et al. 1975

<sup>a</sup>Units are percent sulfuric acid except where indicated otherwise.

<sup>b</sup>mg/m<sup>3</sup> in air

hr = hour; Human-a = asthmatic; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; (WB) = whole-body

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**Ocular Effects.** Accidental contact of the eyes with concentrated sulfuric acid is very destructive and results in devastating injuries including dissolution of the anterior segment of the globe (Grant 1974). Additional complications that have been reported include glaucoma and cataracts. Ocular damage that was limited to external structures (reported as edematous corneas with necrotic epithelium of the cornea, conjunctival, and lids) was reported in a man deliberately splashed with a solution containing concentrated sulfuric acid (Schultz et al. 1968). With the exception of light detection, the man lost vision the day after the exposure. During the next several days his vision improved. The man died from extensive burns and chemical damage to the respiratory tract 5 days after the exposure. Eye damage as a result of contact with sulfuric acid from car batteries has been reported (Holekamp and Becker 1977). Among 93 cases of eye injuries, 9 cases were serious, requiring hospitalization or resulting in permanent damage. In this series of cases, the most common injuries were conjunctival and corneal chemical burns, and iritis. Two-thirds of the injuries occurred when a battery exploded.

As indicated in the section regarding inhalation exposure, contact with sulfuric acid aerosols in air results in ocular irritation. Lacrimation was reported in volunteers exposed to sulfuric acid aerosols (MMD 1.54  $\mu\text{m}$ ) at 20.8 mg/ m<sup>3</sup> (Sim and Battle 1957). The exposures, completed at a relative humidity of 91%, were almost intolerable at the onset. Eye irritation was not reported by subjects exposed to a concentration of 39.4 mg/ m<sup>3</sup> (MMD 0.99  $\mu\text{m}$ ) at a relative humidity of 63%. Because the subjects may have smoked during the exposures, this study is not presented in Table 2-3. Minor eye irritation was significantly increased in asthmatics exposed to 0.999 and 1,460 mg/ m<sup>3</sup> sulfuric acid mist (MMD 0.9  $\mu\text{m}$ ) for 1 hour (Avol et al. 1988). However, statistically significant increases in eye irritation were not reported by healthy subjects exposed to concentrations as high as 1,578 mg/ m<sup>3</sup> under the same conditions.

Sulfuric acid placed directly in the eyes is corrosive. Available animal studies do not agree on the concentration of sulfuric acid required to produce direct eye effects. A 10% (0.1 mL) sulfuric acid solution was considered nonirritating to the eyes when examined in a Draize test in rabbits (Jacobs 1992). Swelling of the iris and “diffuse cornea” were observed in both rats and mice in which 0.01 mL, of a 2.5% sulfuric acid solution was placed in one eye (Sekizawa et al. 1994). The other eye was treated with saline as a control. After treatment, the eyes were kept open for 30 seconds. No effects were observed at concentrations of 1-1.25%.

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In a study in rabbits, 0.1 mL of a 5% (0.5 M; pH 0.6) or 10% (1.02 M; pH 0.1) sulfuric acid solution was placed directly on the cornea of the right eye (Murphy et al. 1982). The left eye served as a control. Directly after treatment, the lid was closed for about 1 second, then released. In 6 of the exposed rabbits at each concentration, the eyes were gently washed for 2 minutes with 300 mL of tap water 30 seconds after exposure. The eyes of another 6 rabbits at each concentration were not washed. Washing had no effect at 10%, a concentration at which severe corneal opacities were observed in 12 of 12 animals. At 5%, minimal corneal opacities were observed in 1 of 6 washed eyes and 2 of 6 unwashed eyes. The effect at 5% was considered minimal and was no longer present 7 days after the exposure. Although washing did not affect the severity of the effect, it did tend to result in an earlier effect following exposure to 5% sulfuric acid. Because the composition of acid is more completely described in the Murphy et al. (1982) study, it is presented in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to sulfuric acid.

### **2.2.3.3 Immunological and Lymphoreticular Effects**

### **2.2.3.4 Neurological Effects**

### **2.2.3.5 Reproductive Effects**

### **2.2.3.6 Developmental Effects**

### **2.2.3.7 Genotoxic Effects**

Genotoxicity studies are discussed in Section 2.5.

### **2.2.3.8 Cancer**

No studies were located regarding cancer in humans or animals after dermal exposure to sulfuric acid.

## **2.3 TOXICOKINETICS**

Toxicokinetic studies regarding sulfur trioxide were not identified. Because sulfur trioxide reacts with water to form sulfuric acid, the toxicokinetics of sulfur trioxide would be expected to be the same as sulfuric acid.

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Sulfuric acid is a direct irritant that results in adverse effects at the site of contact. The effects of sulfuric acid are a result of pH change rather than a result of sulfate. The important toxicokinetic issue is where in the respiratory tract sulfuric acid aerosols will deposit. Factors that help determine the site of deposition in the respiratory tract include environmental conditions, especially relative humidity which affects aerosol size, and physiological factors of the subject including breathing rate, depth of breathing, and method of breathing, e.g., mouth, nose, or oronasal. The effect of hygroscopic growth on deposition within the respiratory tract has been modeled in adults (Martonen and Pate1 1981) and children (Martonen and Zhang 1993). Once in the lung, the sulfur from sulfuric acid has been shown to be rapidly absorbed into the blood stream (Dahl et al. 1983). Sulfate is a metabolite of sulfur amino acids, and excess sulfate is excreted in the urine (Vander et al. 1975).

**2.3.1 Absorption****2.3.1.1 Inhalation Exposure**

The retention of sulfuric acid mist was studied in humans exposed through a face mask to 0.4-1 mg/ m<sup>3</sup> sulfuric acid mist with an average aerosol size of 1 μm (Amdur et al. 1952b). During the 5-15minute exposures, the average retention of the acid aerosols was 77%, with a range of 50-87%.

The clearance of <sup>35</sup>sulfur-labeled sulfuric acid aerosols from the respiratory tract was studied in rats, guinea pigs, and dogs exposed nose-only to 1-20 mg/m<sup>3</sup> (MMAD 0.4-1 .2 μm) for 30 seconds, and in rats and guinea pigs following intranasal installation (Dahl et al. 1983). The results indicated that the sulfur from sulfuric acid is rapidly cleared from the lungs into the blood following inhalation exposure. The lung clearance half-times were 170,230, and 261 seconds in rats, guinea pigs, and dogs, respectively. Very little of the sulfur from the sulfuric acid placed in the nose was absorbed into the rest of the body. Five minutes after treatment, 97.1% and 96.8% of the dose remained in the nose of rats and guinea pigs, respectively. To further study absorption of sulfuric acid by the respiratory tract of dogs, <sup>35</sup>sulfur-labeled sulfuric acid was instilled in one dog 1-2 cm past the nares, in a second generation bronchus of another dog, and in a seventh generation bronchus of a third dog. Clearance from the nasal region was insignificant. Clearance half-time from the second generation bronchus was 200 seconds; from the seventh generation bronchus it was 110 seconds.

### 2.3.1.2 Oral Exposure

No studies were identified regarding the absorption of sulfuric acid following oral exposure of humans or animals.

### 2.3.1.3 Dermal Exposure

No studies were identified regarding the absorption of sulfuric acid following dermal exposure of humans or animals.

## 2.3.2 Distribution

Sulfate is a normal constituent of the blood, with concentrations of 0.8-1.2 mg/dL normally found in the serum of humans (Hensyll990). Concentrations of sulfates in urine range from 53 pmol/dL/Kg in 1-day-old infants to 500 umol/dL/Kg in young men (Lentner 1981). The level of urinary sulfate is a measure of the quantity and quality of proteins in the diet. Studies in which sulfate in blood or urine were measured following exposure to sulfuric acid were not identified.

### 2.3.2.1 Inhalation Exposure

The dose of hydrogen ion delivered to the lungs was estimated in 7 healthy male adults exposed to 0.471 mg/ m<sup>3</sup> sulfuric acid aerosols (MMAD 10 µm) using a head dome that allowed continuous measurement of breathing frequency, tidal volume, and minute ventilation, as well as the onset and persistence of oronasal breathing (Bowes et al. 1995). The 1 -hour exposure period consisted of 40 minutes of rest followed by 20 minutes of moderately heavy exercise on a bicycle ergometer. The amount of hydrogen ion delivered to the lungs was estimated from the total time in minutes of oronasal breathing, the ventilation rate during oral nasal breathing, the hydrogen ion concentration, and the estimated fraction of inhaled air that entered the oral passage during oronasal breathing. Based on an earlier study by this group regarding the lung distribution of 10-µm fog droplets following oronasal breathing, the fractional deposition was assumed to be 85.4% for the oropharynx and 14.6% for the lower airways. The investigators estimated that about 55% of each breath was inhaled orally during oronasal breathing. The estimated amount of hydrogen ion inhaled orally was 6,466±1,778 nmol, with 942±259 nmol penetrating to the lower airways including the larynx, trachea, and bronchopulmonary region. Of the parameters used to estimate the dose delivered to the lung, the

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investigators estimated that the combined physiologic parameters accounted for 70% of the variability (minute ventilation during oronasal breathing, 36%; time in minutes of oronasal breathing, 34%), and the environmental hydrogen ion concentrations accounted for 30% of the variation.

Dosimetric models that examine the effect of hygroscopic growth (increase in aerosol size upon absorption of moisture) within the human respiratory tract on the deposition of sulfuric acid aerosols have been developed. Martonen and Pate1 (1981) modeled sulfuric acid aerosol deposition in the adult, while Martonen and Zhang (1993) modeled deposition in both children and adults at different breathing rates. Both models use the Weibel model A of the human lung which assumes a symmetric dichotomously branching network of airways.

In the Martonen and Pate1 (1981) model, it was assumed that the sulfuric acid droplets reached equilibrium size and density at the entrance to the trachea. Relative humidity in the respiratory tract was assumed to be 100%. Compared to smaller droplets, larger droplets were predicted to grow more as they traversed the respiratory tract. For droplets with initial geometric diameters of 0.01, 0.1, and 1  $\mu\text{m}$  the estimated equilibrium geometric diameters in the respiratory tract were 0.022, 0.72, and 16  $\mu\text{m}$ , respectively. At an inspiratory flow rate of 30 L/minute, the model indicated that total tracheobronchial deposition would be increased for particles with an initial geometric diameter of  $>0.1 \mu\text{m}$ . The increase would result because of increased efficiency of inertial impaction and sedimentation mechanisms. For particles with an initial geometric diameter of  $<0.1 \mu\text{m}$  the model predicted that tracheobronchial deposition would decrease because of reduced efficiency of diffusion with increased particle size.

In the Martonen and Zhang (1993) model, growth of a sulfuric acid droplet was assumed to occur in the first 11 generations of the tracheobronchial tree, with relative humidities increasing from 90% in generation 0, to 99.5% in generation 10. Five subject ages (7, 22, 48, 98, and 240 months) were considered, and the respiratory parameters used for each age are shown in Table 2-4. The model focused on mouth breathing, and sulfuric acid deposition was compared to the deposition of nonhygroscopic iron oxide particles. Total deposition of sulfuric acid droplets in the respiratory tract was greatest for 7-, 22-, and 48-month-old children, and decreased monotonically as the lungs matured. Deposition was also dependent on particle size. When breathing at rest, for particles with an initial geometric diameter of 0.3  $\mu\text{m}$ , hygroscopicity decreased deposition, while for larger particles hygroscopicity increased deposition. For initial particle sizes of 1-2.5  $\mu\text{m}$ , hygroscopicity almost doubled the probability of deposition in the lung. Increased breathing rate through exertion increased the differences in total deposition between children and adults.

**TABLE 2-4. Age-Dependent Respiratory Parameters as a Function of Subject Physical Activity Levels Used in the Martonen and Zhang (1993) Model**

Subject age (months)	Resting		Moderate		Exertion	
	Frequency (min <sup>-1</sup> )	Tidal Volume (mL)	Frequency (min <sup>-1</sup> )	Tidal Volume (mL)	Frequency (min <sup>-1</sup> )	Tidal Volume (mL)
7	35	42	32.0	187	81.1	222
22	28	84	36.9	222	79.9	308
48	22	152	37.3	289	70.4	460
98	18	266	28.4	494	46.5	903
240	14	500	15.5	1,291	24.5	2,449

min<sup>-1</sup> = per minute

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The effects of hygroscopicity and age on the regional deposition of particles were also studied (Martonen and Zhang 1993). At resting respiration rates, deposition of iron oxide particles in the alveolated compartment of the lung peaked at a particle size of 3-5  $\mu\text{m}$  (Martonen and Zhang 1993). While for hygroscopic particles, deposition in the alveolar compartment of the lung peaked at an initial particle size of 1-1.5  $\mu\text{m}$ . Deposition in the alveolar compartment did not change monotonically with age; deposition was highest for the adult and lowest for the 4-month-old child. Breathing rate also changed the regional deposition of particles. For example, in a 4-month-old child at resting breathing rates, deposition of hygroscopic particles with an initial diameter of 1  $\mu\text{m}$  was greatest in the alveolar compartment. During exertion, deposition was greatest in the tracheobronchial region.

The Martonen and Zhang (1993) model indicates that, in addition to particle size, subject age and exertion level should be considered in studies of the health effects of sulfuric acid particles. The model also suggests that children are a sensitive subpopulation for exposure to sulfuric acid aerosols. Martonen and Zhang (1993) cautioned that few general observations regarding the effect of hygroscopicity, age, and breathing rate on the deposition of sulfuric acid aerosols could be made, and that respiratory tract deposition should be considered on a case-by-case basis.

**2.3.2.2 Oral Exposure**

No studies were identified regarding the distribution of sulfuric acid following oral exposure of humans or animals.

**2.3.2.3 Dermal Exposure**

No studies were identified regarding the distribution of sulfuric acid following dermal exposure of humans or animals.

**2.3.3 Metabolism**

Sulfur trioxide in contact with water forms sulfuric acid with the evolution of heat. Further contact with water results in the dissociation of sulfuric acid into hydrogen ions and hydrated sulfate ions, which can combine with other ions that are present in the body. Sulfate does not need to be further metabolized to be excreted in the urine. Route-specific studies of the metabolism of sulfuric acid were not identified.

### **2.3.4 Elimination and Excretion**

Sulfate, which is a normal metabolite of sulfur-containing amino acids, is excreted in the urine (Vander et al. 1975).

#### **2.3.4.1 Inhalation Exposure**

No studies were identified regarding the excretion of sulfuric acid following inhalation exposure of humans or animals.

#### **2.3.4.2 Oral Exposure**

No studies were identified regarding the excretion of sulfates following oral exposure of humans or animals to sulfuric acid.

#### **2.3.4.3 Dermal Exposure**

No studies were identified regarding the excretion of sulfuric acid following dermal exposure of humans or animals.

### **2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**

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

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of

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the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

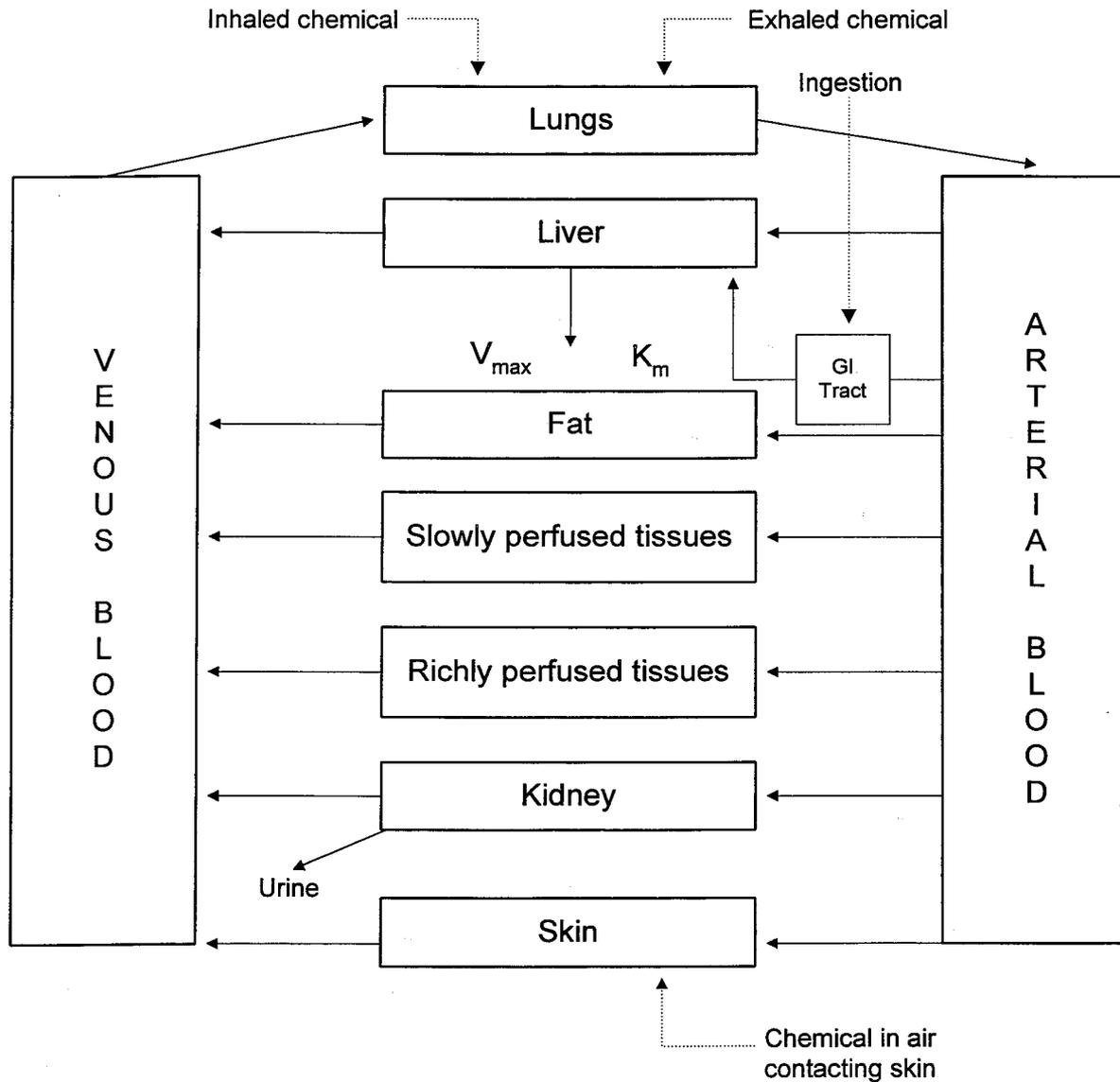
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

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**Figure 2-3. Conceptual Representation of a Physiologically-Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



Note: This is a conceptual representation of a physiologically -based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

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If PBPK models for sulfur trioxide and sulfuric acid exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

PBPK models for sulfur trioxide and sulfuric acid were not identified. Dosimetric models that examine the effect of hygroscopic growth within the respiratory tract on deposition of sulfuric acid aerosols in the lungs are discussed in Section 2.3.2.1.

## 2.4 MECHANISMS OF ACTION

### 2.4.1 Pharmacokinetic Mechanisms

Sulfuric acid is a direct irritant that results in adverse effects at the site of contact. The concentration of sulfuric acid is important in determining effects. For example, a small amount of concentrated sulfuric acid will erode and possibly cause perforation of the gastrointestinal tract if swallowed. The same amount of acid diluted sufficiently will have no effects. The effects of sulfuric acid are thought to be a result of pH change rather than a result of sulfate. If there is enough acid-neutralizing capacity at the site of contact with sulfuric acid, there will be no effects.

For inhalation exposure to sulfuric acid aerosols, the important issues are where in the respiratory tract the aerosols deposit and the duration of exposure. Factors that determine the site of deposition in the respiratory tract include environmental conditions, especially relative humidity which affects aerosol size, and physiological factors of the subject including breathing rate and depth, and method of breathing, e.g., mouth, nose, or oronasal. The effect of hygroscopic growth on deposition within the respiratory tract has been modeled in adults (Martonen and Pate1 1981) and children (Martonen and Zhang 1993). Children may be more sensitive to the respiratory tract effects of sulfuric acid aerosols because pulmonary deposition is increased as a result of smaller airway diameter.

### 2.4.2 Mechanisms of Toxicity

Sulfuric acid aerosol toxicity is dependent on the hydrogen ion content of the aerosol. One mechanism by which sulfuric acid may produce its toxicity is by changing extracellular and intracellular pH. There is evidence that pH plays a critical role in growth control and cell differentiation, and that disrupting the control

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of pH may lead to adverse effects (Soskolne et al. 1989). A sufficiently low pH is genotoxic to some cell systems. Therefore, a significant change in pH produced by sulfuric acid exposure could potentially lead to cellular changes if hydrogen ions reached susceptible targets. A preliminary *in vitro* study that exposed a human tracheal epithelial cell line to sulfuric acid aerosols of 0.75, 1.4, or 3.28  $\mu\text{m}$  for 10 minutes revealed that intracellular pH decreased, and, that at equal mass concentrations, the change in pH was greater for the smaller particle sizes (Chen et al. 1993).

Respiratory mucus serves as a barrier to the penetration of hydrogen ions into the tissue. The buffering capacity and pH of a person's mucus may determine whether there will be a response to a sulfuric acid aerosol exposure. The pH of mucus is generally in the range of 7.4-8.2, and it shows diurnal and day-to-day variations. Asthmatics have been reported to have lower pH mucus, in the range of 5.3-7.6. *In vitro* studies have shown that when the pH of mucus is lowered below about 7.4 the viscosity increases (Holma 1985). Mucus with greater viscosity would serve to decrease mucociliary clearance. It has been estimated that persons with normal mucus buffer capacity and protein content can accommodate about 300  $\mu\text{g}/\text{m}^3$  of sulfuric acid per 30 minutes (Holma 1989).

Rather than a change in viscosity, an animal study suggests that increased mucus thickness may affect clearance. Changes in mucus viscosity were not observed in rats exposed to 94.4  $\text{mg}/\text{m}^3$  for 4 hours, or in guinea pigs exposed to 43.3  $\text{mg}/\text{m}^3$  for 4 hours (Lee et al. 1995). The thickness of the mucus layer was increased in these animals.

Mechanisms of sulfuric acid-induced pulmonary injury have also been studied. Atropine was administered to 12 guinea pigs in order to inhibit reflex-mediated bronchoconstriction and the animals were exposed to 32.6  $\text{mg}/\text{m}^3$  sulfuric acid aerosol (MMAD 1.0  $\mu$ , RH 70-90%) for 4 hours (Brownstein 1980). Unlike guinea pigs who were exposed to sulfuric acid without atropine pre-treatment, the atropine-treated animals had no signs of pulmonary injury, such as epithelial desquamation. It was concluded that pulmonary injury following sulfuric acid exposure may be due in part to mechanical forces generated during reflex-mediated bronchoconstriction.

The genotoxic effects of significantly lowered pH may contribute to the ability of sulfuric acid to produce respiratory tract tumors. It has also been postulated that sulfuric acid may promote carcinogenesis by inducing chronic tissue irritation (Soskolne et al. 1989). Chronic inflammation results in the release of free radicals which have a genotoxic action. In addition, chronic inflammation may increase susceptibility to

infection which may contribute to a carcinogenic response. However, the mechanism of carcinogenesis remains to be proven.

### **2.4.3 Animal-to-Human Extrapolations**

Guinea pigs, which are the most sensitive animal species, are thought to react to sulfuric acid aerosol exposures in a manner similar to asthmatics, the most sensitive segment of the human population (Amdur 1989a). Studies have demonstrated that sulfuric acid has similar effects on mucociliary clearance in rabbits, donkeys, and humans, thus suggesting that these animals may be useful models for extrapolation to humans (Gearhart and Schlesinger 1989; Schlesinger et al. 1979).

## **2.5 RELEVANCE TO PUBLIC HEALTH**

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

### **Overview**

Sulfuric acid, which forms in the atmosphere from sulfur dioxide, is a common atmospheric pollutant. Sulfur trioxide is an intermediate in the formation of sulfuric acid from sulfur dioxide. The effects of sulfuric acid are a result of hydrogen ion and not sulfate. The potential for other substances, especially ammonia, in the atmosphere to neutralize sulfuric acid determines whether or not humans are exposed to sulfuric acid aerosols.

Numerous experimental acute-duration exposure studies of humans and animals indicate that exposure to sulfuric acid aerosols can result in changes in lung function and can affect clearance of particles from the respiratory tract. In addition to exposure concentration, the response to sulfuric acid is also dependent on the size of the aerosol, relative humidity (Sim and Pattle 1957), the buffering capacity of the aerosol (Fine et al. 1987), respiratory tract ammonia levels (Utell et al. 1989), as well as the breathing pattern of the subject (Bowes et al. 1995). Children are generally more sensitive to sulfuric acid aerosols than adults, and asthmatic individuals are more sensitive than healthy subjects. The lowest concentrations and exposure durations resulting in transient changes in pulmonary function tests in asthmatics were a 40-45 minute exposure to  $0.07 \text{ mg/ m}^3$  (MMAD  $0.72 \text{ }\mu\text{m}$ ) (Hanley et al. 1992) and a 50-minute exposure to  $0.1 \text{ mg/ m}^3$  (MMAD

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0.6  $\mu\text{m}$ ) (Koenig et al. 1985). The effects noted included a transient decrease in FVC, a decrease in FEV<sub>1</sub>, and increased respiratory resistance. Other studies of pulmonary function in asthmatics exposed to similar concentrations of sulfuric acid have not shown adverse effects (Anderson et al. 1992; Avol et al. 1990; Koenig et al. 1992; Utell et al. 1983). The most sensitive effect in normal subjects is clearance of test particles of sizes in the range of 3-7.6  $\mu\text{m}$ . A concentration of about 0.1 mg/ m<sup>3</sup> has resulted in a reduced rate of bronchial mucociliary clearance in normal subjects (Laube et al. 1993; Spektor et al. 1989).

Acute studies in animals exposed to sulfuric acid aerosols have also shown changes in pulmonary function tests (Amdur 1958; Amdur et al. 1978) and clearance of test particles (Chen and Schlesinger 1983; Gearhart and Schlesinger 1989; Mannix et al. 1991; Schlesinger et al. 1984). Guinea pigs are more sensitive to changes in pulmonary function than other species and are thought to respond in a manner similar to asthmatic humans (Amdur 1989a).

In the United States, sulfuric acid or hydrogen ion (as sulfuric acid) levels in the atmosphere are generally below 0.005 mg/ m<sup>3</sup> (Lioy and Waldman 1989), although higher concentrations, up to about 0.7 mg/ m<sup>3</sup>, can occur during pollution episodes (Amdur 1989b). Epidemiological studies do not provide clear evidence linking environmental exposure to sulfuric acid aerosols alone to adverse health effects in humans (Lioy and Waldman 1989).

More sulfuric acid is produced in the United States than any other chemical (C&EN 1996). Therefore, there is a high potential for accidental and occupational exposure to sulfuric acid. Among states reporting accidental events during the time period 1990-1996 (5 states 1990-1991, 9 states 1992-1994, 14 states 1995-1996) 905 events occurred which involved only sulfuric acid and oleum (3 oleum releases), and 173 events occurred which involved mixtures or multi-chemical releases that included sulfuric acid or oleum (HSEES 1997). Among the events in which only sulfuric acid and oleum were released, 53 required evacuation (information not available for 39 events), there was 1 death, and a total of 203 victims. Chemical burns (38.5%), respiratory irritation (21.6%), and eye irritation (15.4%) were the most frequently reported effects following these releases. Among the mixture or multi-chemical releases that included sulfuric acid or oleum, 40 required evacuation (information not available for 3 events), there were 3 deaths, and a total of 322 victims. The most frequently reported effects following the release of mixtures were respiratory irritation (56.5%), eye irritation (17.8%), and nausea and vomiting (5.1%).

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Industries with potential exposure to sulfuric acid include fertilizer, sulfuric acid, isopropanol, synthetic ethanol, and detergent production; building and construction; electric and electronic equipment; food products; health services; leather; oil and gas extraction; petroleum and coal products; photography shops; printing and publishing; paper and allied products; rubber and plastic products; steel; and textile products (IARC 1992). In occupational settings, exposure can be above  $0.5 \text{ mg/ m}^3$ , with the highest concentrations generally found in metal pickling operations. Effects observed in persons occupationally exposed to sulfuric acid included a slight increase in bronchitis without a change in lung function (Williams 1970), a small decrease in FVC (Gamble et al. 1984b), tooth erosion (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961), and an increase in periodontal pockets (Tuominen 1991). The lowest average concentration resulting in effects in these occupational studies was  $0.2 \text{ mg/ m}^3$  (Gamble et al. 1984b). However, in the remaining occupational studies, effects were observed primarily at concentrations which exceeded the OSHA permissible exposure limit (1996) for sulfuric acid aerosols of  $1 \text{ mg/ m}^3$  (El-Sadik et al. 1972; Malcolm and Paul 1961; Williams 1970).

Chronic-duration inhalation studies in monkeys exposed to sulfuric acid aerosols reported histopathological changes in the lungs at  $0.38 \text{ mg/ m}^3$  (MMD  $2.15 \mu\text{m}$ ),  $2.45 \text{ mg/ m}^3$  (MMD  $3.6 \mu\text{m}$ ), and  $4.79 \text{ mg/ m}^3$  (MMD  $0.73 \mu\text{m}$ ), with no effects at  $0.48 \text{ mg/ m}^3$  (MMD  $0.54 \mu\text{m}$ ) (Alarie et al. 1973). Arterial oxygen was affected only at  $2.45 \text{ mg/ m}^3$  (MMD  $3.6 \mu\text{m}$ ), the only exposure concentration utilized in these studies that resulted in histopathologic changes in the alveoli. Chronic exposure of guinea pigs at concentrations up to  $0.9 \text{ mg/ m}^3$  (MMD  $0.49 \mu\text{m}$ ) did not result in any histopathological changes in the lungs (Alarie et al. 1973, 1975). Additional treatment-related adverse effects on other organ systems were not observed in either monkeys or guinea pigs, although all the data were not presented.

Inhalation exposure to sulfuric acid aerosols has not been shown to result in reproductive or developmental effects in mice or rabbits (Murray et al. 1979). Because sulfuric acid is a direct-acting toxicant and not likely to reach reproductive organs or the fetus, reproductive and developmental effects are unlikely to occur in humans exposed to sulfuric acid.

Occupational exposure to mineral acid aerosols including sulfuric acid has been associated with respiratory tract cancers (Alderson and Rattan 1980; Beaumont et al. 1987; Coggon et al. 1996; Cookfair et al. 1985; Forastiere et al. 1987; Houghton and White 1994; Soskolne et al. 1982, 1984, 1992; Steenland and Beaumont 1989; Steenland et al. 1988). However, most of the cancers were in smokers who were also exposed to other chemicals. There is no information that exposure to sulfuric acid by itself is carcinogenic,

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and there is no clear data on exposure concentrations of sulfuric acid associated with cancer in humans. DHHS (1994) and EPA have not classified sulfur trioxide or sulfuric acid for carcinogenic effects. Based on the limited human data, which associate occupational exposure to mineral acid aerosols with the development of lung and laryngeal cancers, IARC (1992) considers occupational exposure to strong inorganic acid mists containing sulfuric acid carcinogenic to humans (Group 1). The carcinogenicity of sulfuric acid alone has not been classified by IARC. The carcinogenicity of sulfuric acid has not been studied in animals.

In addition to inhalation exposure to sulfuric acid aerosols, there is potential for accidental oral or dermal exposure to concentrated sulfuric acid. Sulfuric acid is found in lead-acid batteries and concentrated drain cleaners. Some home cleaners (especially toilet bowl cleaners) contain compounds that release sulfuric acid when they contact water. Therefore, the general population may come into contact with sulfuric acid when using these products. At sufficient concentrations, sulfuric acid has been shown to corrode the gastrointestinal tract when swallowed (Aktug et al 1995; Dilawari et al. 1984) and corrode the skin (Branday et al. 1996) and eyes (Grant 1974; Holekamp and Becker 1977; Schultz et al. 1968) on contact.

### **Minimal Risk Levels for Sulfur Trioxide/Sulfuric Acid**

#### ***Inhalation MRLs***

No inhalation MRLs were derived for sulfur trioxide or sulfuric acid exposure. The only inhalation study regarding sulfur trioxide exposure is a report of respiratory irritation in persons accidentally exposed (Stueven et al. 1993). Exposure concentrations were not provided in this report.

Several acute-duration human exposure studies have reported respiratory effects including bronchoconstriction resulting in changes in lung function tests and changes in bronchial mucociliary clearance. The lowest concentration that resulted in changes in lung function tests was  $0.07 \text{ mg/ m}^3$  (MMAD  $0.72 \text{ }\mu\text{m}$ ), a concentration at which transient decreases in FVC and  $\text{FEV}_1$  were observed in asthmatics exposed for 40-45 minutes with intermittent exercise (Hanley et al. 1992). Increased respiratory resistance, decreased maximum flow at 50% and 75% of total vital capacity, and decreased  $\text{FEV}_1$  have also been reported in asthmatics exposed to  $0.1 \text{ mg/ m}^3$  (MMAD  $0.6 \text{ }\mu\text{m}$ ) for 50 minutes with exercise (Koenig et al. 1985). Although asthmatics are considered more sensitive to changes in lung function following exposure to sulfuric acid, all studies have not reported changes in lung function tests in asthmatics exposed to sulfuric acid aerosols. For example, changes in lung function tests were not observed in asthmatics exposed to

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0.01 mg/m<sup>3</sup> sulfuric acid aerosols (MMAD 0.5 μm) for 1 hour with intermittent exercise (Anderson et al. 1992). Lung function was affected in 1 of the 15 exposed subjects leading the study authors to conclude that there may be a subgroup of asthmatics that are more sensitive to sulfuric acid exposure. Bronchial mucociliary clearance has only been studied in normal individuals. Decreased clearance was observed in subjects exposed to sulfuric acid aerosols (MMD 0.5 μm) with a nasal mask for 1 hour at 0.98 mg/ m<sup>3</sup> for test particles of 7.6 μm (Leikauf et al. 1981), and at 0.108 mg/ m<sup>3</sup> for test particles of 4.2 μm (Leikauf et al. 1984).

These studies are not being used as the basis of an MRL because physiological factors and conditions under which humans are exposed are just as important in determining the response to sulfuric acid aerosols as the aerosol concentration and aerosol size. Factors which will affect the response to sulfuric acid include aerosol size, relative humidity, condition of the subject (e.g., asthmatic), amount of ammonia present in the mouth, breathing rate, and depth of breathing. Difficulties in estimating doses of hydrogen ion were demonstrated by Bowes et al. (1995). The hydrogen ion dose to the lower airways of healthy male adults was estimated following exposure to 0.471 mg/ m<sup>3</sup> sulfuric acid aerosol (MMAD 10 μm) through a head dome for 1 hour (40 minutes of rest and 20 minutes of exercise). Concentrations of sulfuric acid and physiological parameters, such as respiratory rate, tidal volume, minute ventilation and duration of oronasal breathing, were factors used in calculations to estimate doses. Estimated doses of hydrogen ion were variable among subjects, and about 30% of the variability was due to inconsistencies in the sulfuric acid concentrations of aerosols. The majority of variability, 70%, was due to physiological parameters, primarily duration of and minute ventilation during oronasal breathing. The authors stated the importance of calculating hydrogen ion doses in such studies in order to avoid false impressions of increased sensitivity in subjects who receive larger doses. Because the response to sulfuric acid aerosol exposure is so dependent on individual factors rather than exposure concentrations it would be very difficult to identify a NOAEL for human exposure.

Intermediate-duration inhalation studies are limited to animal studies (Fujimaki et al. 1992; Gearhart and Schlesinger 1986; Lewis et al. 1969; Schlesinger et al. 1979; Thomas et al. 1958), and chronic-duration inhalation studies include human occupational studies (El-Sadik et al. 1972; Gamble et al. 1984; Kitagawa 1984; Kremer et al. 1994; Malcolm and Paul 1961; Williams 1970) and animal studies (Alarie et al. 1973, 1975; Schlesinger et al. 1992a). Because the occupational studies identified NOAELs higher than LOAELs in acute-duration studies they were not considered appropriate for MRL derivation. The methodology for extrapolating from inhalation exposure of animals to hygroscopic aerosols has yet to be developed (EPA 1994). Therefore, inhalation MRLs could not be developed from animal studies.

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**Oral MRLs**

No oral MRLs for sulfuric acid were derived. Although high concentrations of sulfuric acid are corrosive to the gastrointestinal tract (Aktug et al. 1995; Dilawari et al. 1984), there were insufficient data regarding oral exposure to sulfuric acid for the development of oral MRLs. This profile did not consider the oral toxicity of sulfites, which are used as food preservatives, or the oral toxicity of sulfate-containing compounds.

**Death**

Studies regarding death of humans following acute- and intermediate-duration inhalation exposure to sulfuric acid aerosols were not identified. Increased mortality, especially of elderly persons and those with preexisting cardiac and respiratory disease, has been reported during or shortly after air pollution episodes (Costa and Amdur 1996). Because it is not possible to clearly separate the effects of sulfuric acid aerosols from other pollutants including particulates, sulfur dioxide, and ozone, these studies are not discussed further. Deaths of humans have been reported following acute oral (Dilawari et al. 1984) and dermal exposure (Branday et al. 1996; Schultz et al. 1968).

One-hour LC<sub>50</sub>s of 347 and 420 ppm fuming sulfuric acid have been reported for female and male rats, respectively (Vernot et al. 1977). The lowest concentration of sulfuric acid aerosols that resulted in the death of rats was 383 mg/ m<sup>3</sup> (Treon et al. 1950). Mice were more susceptible to sulfuric acid aerosol exposure (diameter 1-2 μm) than rats (Treon et al. 1950). Among the species exposed to sulfuric acid aerosols, guinea pigs are the most sensitive. During a 1-hour exposure to 52-61 mg/ m<sup>3</sup> sulfuric acid (MMAD 0.8-2.1 μm), about 6% of the exposed guinea pigs died (Stengel et al. 1993). Younger guinea pigs are more sensitive to sulfuric acid aerosols than older guinea pigs (Amdur et al. 1952a).

The effect of aerosol size on survival of guinea pigs exposed to sulfuric acid aerosols has been studied. Following exposure to sulfuric acid aerosols with MMADs of 0.8 and 0.4 μm, LC<sub>50</sub>s of 30.3 and >109 mg/ m<sup>3</sup>, respectively, were reported for guinea pigs exposed for 8 hours (Wolff et al. 1979). Eight-hour LC<sub>50</sub>s of 59.8 and 27.3 mg/ m<sup>3</sup> were reported for aerosols of MMADs of 0.8 and 2.7 μm, respectively (Pattle et al. 1956).

No effect on survival was observed in cynomolgus monkeys or guinea pigs exposed to sulfuric acid aerosols 23.3 hours/day, 7 days/week, for 78 weeks (monkeys) or 52 weeks (guinea pigs) (Alarie et al. 1973).

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The LD<sub>50</sub> in rats treated by gavage with reagent grade sulfuric acid in water at a concentration of 0.25 g/mL was reported as 2,140 mg/kg (Smyth et al. 1969). Deaths of laboratory animals following longer-term oral exposure to sulfuric acid were not reported. No studies were located regarding deaths in animals after dermal exposure to sulfuric acid. Deaths are unlikely to occur at concentrations of sulfuric acid normally found in the environment or at hazardous waste sites.

**Systemic Effects**

**Respiratory Effects.** Acute inhalation exposure to sulfur trioxide and sulfuric acid results in respiratory tract irritation in humans (Sim and Pattle 1957; Stueven et al. 1993) and animals (Stengel et al. 1993; Wolff et al. 1979). At lower concentrations acute inhalation exposure adversely affects pulmonary function tests in both humans (Avol et al. 1988; Hanley et al. 1992; Koenig et al. 1992; Utell et al. 1983) and animals (Amdur 19.58, 1959; Amdur et al. 1978; Kobayashi and Shinozaki 1993). Adolescent asthmatics are the humans most sensitive to sulfuric acid aerosol exposure (Hanley et al. 1992; Koenig et al. 1992), and guinea pigs, which are thought to react in a manner similar to asthmatic humans, are the most sensitive of animal species tested (Amdur 1989a). The lowest concentrations and exposure durations resulting in transient changes in pulmonary function tests in adolescent asthmatics were a 40-45-minute exposure to 0.07 mg/m<sup>3</sup> (Hanley et al. 1992) and a 50minute exposure to 0.1 mg/ m<sup>3</sup> (Koenig et al. 1985). The effects noted included a transient decrease in FVC, a decrease in FEV<sub>1</sub>, and increased respiratory resistance. Other studies of pulmonary function in asthmatics exposed to similar concentrations of sulfuric acid have not shown adverse effects (Anderson et al. 1992; Avol et al. 1990; Koenig et al. 1992). Factors that affect the respiratory response to sulfuric acid aerosols include aerosol size, relative humidity (Sim and Pattle 1957), the buffering capacity of the aerosol (Fine et al. 1987), respiratory tract ammonia levels (Utell et al. 1989), as well as the breathing pattern of the subject (Bowes et al. 1995).

A sensitive effect of sulfuric acid exposure in healthy subjects is clearance of test particles. Exposure to concentrations of 0.98-0.11 mg/m<sup>3</sup> has resulted in a reduced rate of bronchial mucociliary clearance in healthy subjects (Leikauf et al. 1981, 1984; Spektor et al. 1989). Clearance of test particles has also been shown to be adversely affected in animals following both acute- and intermediate-duration exposures (Chen and Schlesinger 1983; Gearhart and Schlesinger 1989; Mannix et al. 1991; Schlesinger and Gearhart 1986; Schlesinger et al. 1979,1984). It has been suggested that decreased clearance induced by some exposures to sulfuric acid aerosols may contribute to the development of chronic bronchitis (Lippmann et al. 1982).

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Epidemiological studies do not provide clear evidence of adverse respiratory effects in humans following environmental exposure to sulfuric acid (Abbey et al. 1993,1995; Lioy and Waldman 1989). Respiratory effects observed in persons occupationally exposed to sulfuric acid aerosols include a slight increase in bronchitis without a change in lung function (Williams 1970) and a small decrease in FVC (Gamble et al. 1984b). The lowest average concentration resulting in effects in these occupational studies was 0.2 mg/m<sup>3</sup> (Gamble et al. 1984b).

Chronic-duration inhalation studies in monkeys exposed to sulfuric acid aerosols reported histopathological changes in the lungs at 0.38 mg/m<sup>3</sup> (MMD 2.15 μm), 2.45 mg/m<sup>3</sup> (MMD 3.6 μm), and 4.79 mg/m<sup>3</sup> (MMD 0.73 μm). with no effects at 0.48 mg/m<sup>3</sup> (MMD 0.54 μm) (Alarie et al. 1973). The 2.45mg/m<sup>3</sup> exposure concentration also resulted in decreased arterial oxygen and was the only exposure in which the histopathological changes also involved the alveoli. Chronic exposure of guinea pigs at concentrations up to 0.9 mg/m<sup>3</sup> (MMD 0.49 μm) did not result in any histopathological changes in the lungs (Alarie et al. 1973, 1975).

In the United States, sulfuric acid or hydrogen ion (as sulfuric acid) levels in the atmosphere are generally below 0.005 mg/m<sup>3</sup> (Lioy and Waldman 1989), although higher concentrations, up to about 0.7mg/ m<sup>3</sup>, can occur during pollution episodes (Amdur 1989b). Therefore, during some pollution episodes, asthmatic subjects may respond with decrements in pulmonary function tests, and decreases in mucociliary clearance may occur in both normal and asthmatic subjects. Exercise, which increases breathing rate and oral breathing, increases the response to sulfuric acid aerosols.

Following oral exposure to sulfuric acid, death resulting from bronchopneumonia occurred in one subject (Dilawari et al. 1984). This case suggests that oral exposure to sulfuric acid could result in aspiration of the acid into the lungs leading to respiratory effects. Respiratory effects have not been reported following dermal exposure to sulfuric acid.

**Cardiovascular Effects.** Acute occupational exposure to 35% fuming sulfuric acid has resulted in abnormal ventricular activity (Goldman and Hill 1953). However, limited human studies (Abbey et al. 1995; Bowes et al. 1995), and the lack of histopathological changes in the hearts of monkeys and guinea pigs exposed chronically, suggest that inhalation exposure to atmospheric concentrations of sulfuric acid aerosols does not result in cardiovascular effects. No studies were identified regarding cardiovascular effects of sulfur trioxide

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or sulfuric acid following exposure via other routes. Sulfuric acid is a direct-acting toxicant. Therefore, cardiovascular effects are not likely to occur following exposure to sulfuric acid pollution in air.

***Gastrointestinal Effects.*** Studies reporting accidental ingestion of concentrated sulfuric acid by humans indicate that it erodes the gastrointestinal tract if it is swallowed (Aktug et al. 1995; Dilawari et al. 1984). The concentration of acid required to cause gastrointestinal erosion has not been studied. Gastrointestinal effects have not been studied in animals, nor have they been studied following exposure via other routes. Because sulfuric acid is not likely to be present at high concentrations in the environment, environmental exposure to sulfur trioxide or sulfuric acid is unlikely to result in gastrointestinal tract effects.

***Hematological Effects.*** Hematological effects have not been reported in humans following acute inhalation exposure to sulfuric acid (Chaney et al. 1980). There are no known studies of hematological effects following oral or dermal exposure. Hematological effects have not been reported in monkeys (Alarie et al. 1973) or guinea pigs (Alarie et al. 1973, 1975) following chronic inhalation exposure to sulfuric acid aerosols. Because sulfuric acid is a direct-acting toxicant, hematological effects are not likely to occur following exposure to sulfur trioxide or sulfuric acid by any route.

***Musculoskeletal Effects.*** Musculoskeletal effects have not been studied in humans exposed to sulfur trioxide or sulfuric acid, nor have they been studied by any other route of exposure. Because sulfuric acid is a direct-acting toxicant, musculoskeletal effects are not likely to occur following exposure by any route.

The effect of sulfuric acid on growth, including tibia length, has been studied in chicks (Capdevielle and Scanes 1995b) and ducklings (Capdevielle and Scanes 1995a) treated with the acid in the diet. Decreased tibia length associated with decreased food intake was observed in chicks but not ducklings. The objective of these studies was to determine whether aluminum (or acid, which increases aluminum levels in the environment) affects the growth of birds. Aluminum was shown to have an effect on growth of chickens that could not be attributed to the changes in food intake, while the effects of acid were attributed to decreased food intake. Although sulfuric acid may not have a direct effect on growth, including bone length, in the environment, lowered pH may lead to secondary effects by increasing levels of metals including aluminum.

***Hepatic Effects.*** Hepatic effects have not been reported in humans following acute inhalation exposure of sulfuric acid (Chaney et al. 1980). There are no known studies of hepatic effects following oral or dermal exposure.

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Effects on the liver have not been observed in mice or rabbits following inhalation exposure to sulfuric acid during gestation (Murray et al. 1979), or in monkeys (Alarie et al. 1973) or guinea pigs (Alarie et al. 1973, 1975) following chronic inhalation exposure to sulfuric acid. Liver weights were not affected in chicks (Capdevielle and Scanes 1995b) or ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. Because sulfuric acid is a direct-acting toxicant, hepatic effects are not likely to occur following exposure by any route.

**Renal Effects.** Renal effects have not been studied in humans exposed to sulfur trioxide or sulfuric acid by any route.

Microscopic changes in the kidneys were not observed in monkeys (Alarie et al. 1973) or guinea pigs (Alarie et al. 1973, 1975) following chronic inhalation exposure to sulfuric acid. Kidney weights were not affected in chicks (Capdevielle and Scanes 1995b) or ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. Because sulfuric acid is a direct-acting toxicant, renal effects are not likely to occur following exposure by any route.

**Endocrine Effects.** Endocrine effects have not been studied in humans exposed to sulfur trioxide or sulfuric acid by any route of exposure.

Changes in growth hormone, insulin-like growth factor, and insulin-like growth-factor binding proteins were not observed in chicks (Capdevielle and Scanes 1995b) or ducklings (Capdevielle and Scanes 1995b) fed sulfuric acid in the diet. The objective of these studies was to determine whether aluminum (or acid, which increases aluminum levels in the environment) affects the growth of birds. High doses of aluminum were shown to reduce the levels of insulin-like growth factor in chicks. Although sulfuric acid may not have a direct effect on growth, in the environment, lowered pH may lead to secondary effects by increasing levels of metals including aluminum. Because sulfuric acid is a direct-acting toxicant, endocrine effects are not likely to occur in humans following exposure by any route.

**Dermal Effects.** Direct application of concentrated sulfuric acid to the skin or eyes can result in burns in humans (Branday et al. 1996; Schultz et al. 1968) and animals (Sekizawa et al. 1994). The concentration required to result in dermal burns has not been clearly determined. Dermal exposure of humans to a 10% sulfuric acid solution was considered nonirritating (Nixon et al. 1975).

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Erosion of the skin at 10%, erythema and edema at 5%, and no effects at 2.5% were reported in rats and mice in which sulfuric acid was placed on the electric razor-shaved skin of the back (Sekizawa et al. 1994). No skin effects were observed in guinea pigs or rabbits in which a 10% sulfuric acid solution was applied to the skin (Nixon et al. 1975). During a 4-hour exposure, sulfuric acid was not corrosive to the skin when 0.5 mL of a 4% solution was placed on the backs of rabbits, whose hair was clipped 24 hours before exposure (Vemot et al. 1977). In an in vitro study, application of a 40% solution to rat skin caused a large fall in the transcutaneous electrical resistance (Botham et al. 1992). This response correctly predicts that sulfuric acid is corrosive (Botham et al. 1992).

Dermal effects have not been studied by other routes of exposure. Very high concentrations of sulfur trioxide or sulfuric acid aerosols in the air could potentially result in direct skin irritation. Because these same concentrations would also result in respiratory tract and eye irritation, skin effects would be the prominent effect of sulfuric acid aerosols only if the exposed persons were using respiratory and eye protective equipment.

**Ocular Effects.** Direct exposure of the eyes to concentrated sulfuric acid can result in devastating destruction of the eye (Grant 1974; Holekamp and Becker 1977; Schultz et al. 1968). Direct exposure of the eyes to lower concentrations results in transient injury with complete recovery (Grant 1974). Eye irritation including lacrimation has been reported in humans exposed to sulfuric acid in air (Avol et al. 1988; Sim and Pattle 1957). The effect was worse at high humidity than at low humidity (Sim and Pattle 1957).

Animal studies indicate that direct application of sulfuric acid into the eyes is corrosive (Murphy et al. 1982; Sekizawa et al. 1994). The concentration of sulfuric acid required to result in direct eye effects has not been clearly defined. A concentration of 10% was considered nonirritating in rabbits in one study (Sekizawa et al. 1994) while a 10% concentration resulted in severe corneal opacities in rabbits with minimal effects observed at 5% in a second study (Murphy et al. 1992). Ocular effects are unlikely to occur at the levels of sulfuric acid that are found in the environment. However, during episodes of high pollution, levels of sulfuric acid could be high enough to cause eye irritation.

**Body Weight Effects.** No effects on body weight were observed in mice or rabbits following inhalation exposure to sulfuric acid aerosols during gestation (Murray et al. 1979), or in monkeys (Alarie et al. 1973) or guinea pigs (Alarie et al. 1973, 1975) following chronic exposure to sulfuric acid aerosols.

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Decreased body weight gain associated with decreased food intake was observed in chicks (Capdevielle and Scanes 1995b) but not ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. The objective of these studies was to determine if aluminum (or acid, which increases aluminum levels in the environment) affects the growth of birds. Aluminum was shown to have an effect on growth of chickens that could not be attributed to changes in food intake; while the effects of acid were attributed to decreased food intake. Although sulfuric acid may not have a direct effect on growth, in the environment, lowered pH may lead to secondary effects by increasing levels of metals including aluminum.

Body weight changes have not been studied in animals dermally exposed to sulfuric acid. Because sulfuric acid is a direct toxicant, body weight changes are unlikely following dermal exposure, except possibly as a secondary effect as a result of the stress of dermal burns.

***Other Systemic Effects.*** Studies of workers indicate that exposure to sulfuric acid aerosols can result in lowered pH of the saliva (El-Sadik et al. 1972), erosion of the teeth (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961), and increased prevalence of periodontal pockets (Tuominen 1991). Malcolm and Paul (1961) indicated that the front teeth were the teeth most often affected, suggesting that the effect was the result of direct impingement of acid mist on the teeth. Tooth erosion is unlikely to occur at sulfuric acid concentrations generally found in the environment.

***Immunological and Lymphoreticular Effects.*** The function of alveolar macrophages collected from humans following inhalation exposure to sulfuric acid aerosols for 2 hours was not affected (Frampton et al. 1992). Alveolar macrophage function was affected in animals following inhalation exposure to sulfuric acid aerosols, resulting in decreased intracellular pH (Chen et al. 1995) depressed phagocytic activity (Chen et al. 1992a; Schlesinger et al. 1992b), and reduced TNF cytotoxic activity and zymosan-stimulated production of superoxide anion (Schlesinger et al. 1992b; Zelikoff and Schlesinger 1992). These effects on alveolar macrophage function have not been shown to be concentration related. Once a critical level of sulfuric acid was reached, no further effects were observed. Effects were greater following exposure to smaller aerosols (MMD 0.04  $\mu\text{m}$  versus 0.3  $\mu\text{m}$ ), leading Chen et al. (1992a) to suggest that the smaller droplets deliver a higher dose to the macrophages than the larger droplets.

Inhalation exposure to sulfuric acid aerosols has also been shown to enhance antigen-induced histamine release from mast cells collected from exposed guinea pigs (Fujimaki et al. 1992). Mice challenged with

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*Streptococcus pyrogens* directly after ultrafine sulfuric acid aerosol exposure (2 hours/day for 5 days) did not show increased mortality (Grose et al. 1982).

The studies of immune system function in animals suggest that although sulfuric acid exposure may adversely affect *in vitro* function of macrophages collected from exposed animals, the ability to defend against bacterial infections may not be adversely affected by inhalation exposure to sulfuric acid aerosols. Immunological and lymphoreticular effects have not been studied following oral or dermal exposure to sulfuric acid. Because sulfuric acid is a direct-acting toxicant, system-wide effects on the immune system are not likely following exposure to sulfuric acid by any route.

**Neurological Effects.** Lightheadedness and dizziness have been reported by persons accidentally exposed to unspecified concentrations of sulfur trioxide (Stueven et al. 1993). Fatigue and headaches were reported more frequently in asthmatic volunteers when they were exposed to sulfuric acid aerosols at 0.999 but not 0.396 mg/ m<sup>3</sup> for 1 hour (Avol et al. 1988). In guinea pigs, uncoordinated movement was reported after exposure to 165 mg/ m<sup>3</sup> of sulfuric acid mists but not higher concentrations. Neurological effects have not been studied following oral or dermal exposure of humans and animals to sulfuric acid. Because sulfuric acid is a direct-acting toxicant, neurological effects other than subjective symptoms and reflex response to pain are not likely following exposure to sulfuric acid by any route.

**Reproductive Effects.** No significant effects on the mean numbers of implants/dam or resorptions/litter were noted in mice or rabbits exposed by inhalation to sulfuric acid aerosols during gestation (Murray et al. 1979). Changes in testes weight were not observed in chicks (Capdevielle and Scanes 1995b) or ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. Additional studies regarding reproductive effects of sulfuric acid in humans or animals exposed by any route were not identified. Because sulfuric acid is a direct-acting toxicant, reproductive effects are not likely following exposure to sulfuric acid by any route.

**Developmental Effects.** Significant effects on fetal body weights or on the incidence of major or minor malformations were not observed in mice or rabbits exposed by inhalation to sulfuric acid aerosols during gestation (Murray et al. 1979). No additional studies were identified regarding developmental effects of sulfuric acid in humans or animals following exposure by any route. *In vitro* studies have shown that sulfuric acid, or decreased pH, can induce chromosomal aberrations. Because sulfuric acid is a direct-acting toxicant, developmental effects in mammals are not likely following exposure by any route. Genotoxicity is possible

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only if hydrogen ions come into direct contact with a cell. During inhalation or dermal exposure, hydrogen ions are not absorbed and distributed throughout the systemic circulation, and will not contact germ cells. However, developing organisms that are in direct contact with the environment (e.g., insects, amphibians) could be adversely affected if there are sufficient levels of sulfuric acid to result in decreased pH.

**Genotoxic Effects.** In viva studies regarding the genotoxicity of sulfuric acid were not identified. In vitro studies regarding the genotoxicity of sulfuric acid are summarized in Table 2-5. Sulfuric acid did not increase gene mutation in *Escherichia coli*, which was tested only without metabolic activation (Demerec et al. 1951). In *Salmonella typhimurium* (strains TA97, TA98, TA100, TA102, and TA1535) sulfuric acid was negative both with and without rat S9 metabolic activation (Cipollaro et al. 1986).

Increases in chromosomal aberrations were observed in root meristematic tissue of the plant *Vicia faba* (Zura and Grant 1981) and in Chinese hamster ovary cells (Morita et al. 1989) exposed to sulfuric acid. In a study on the effect of pH on the induction of mitotic aberrations in sea urchins (*Sphaerechinus granduris*, *Purucentrotus lividus*), an increase in aberrations was observed at pH  $\leq 6.5$  (Cipollaro et al. 1986). A similar genotoxic effect was observed with sulfuric acid, hydrochloric acid, and phosphoric acid. These results indicate that pH rather than sulfate was responsible for the effect.

Studies have demonstrated that genotoxicity is associated with an acidic pH level. At pH values (pH adjusted with lactic acid) of 6.5-7.0 the number of chromosomal anomalies in human lymphocytes *in vitro* was significantly increased compared with cells cultured at pH 7.5 (Shimada and Ingalls 1975). The anomalies observed included hypodiploidies, hyperdiploidies, and endoreduplications. In mouse lymphoma L5178Y TK<sup>+/+</sup> cells, pH of 6-6.8 (adjusted with hydrochloric acid) plus S9 resulted in an increase in mutations and chromosomal aberrations (Cifone et al. 1987). A transformed-like morphology was induced in Syrian hamster cells grown at pH values  $< 6.9$  (LeBoeuf and Kerckaert 1986).

**Cancer.** Occupational exposure to sulfuric acid aerosols along with other chemicals has been associated with the development of respiratory tract cancers, especially laryngeal and lung cancers (Alderson and Rattan 1980; Beaumont et al. 1987; Coggon et al. 1996; Cookfair et al. 1985; Forastiere et al. 1987; Houghton and White 1994; Soskolne et al. 1982, 1984, 1992; Steenland and Beaumont 1989; Steenland et al. 1988). However, most of the cancers were in smokers who were also exposed to other chemicals. Following a review of 25 epidemiological studies, Sathiakumar et al. (1997) concluded that there is a moderate association between sulfuric acid exposure and laryngeal cancer. Most studies were limited because of unquantified

Table 2-5. Genotoxicity of Sulfuric Acid *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Escherichia coli</i>	Gene mutation	Not tested	–	Demerec et al. 1951
<i>Salmonella typhimurium</i> (TA97, TA98, TA102, TA1535)	Gene mutation	–	–	Cipollaro et al. 1986
Eukaryotic organisms:				
<i>Vicia faba</i> (plant)	Chromosomal aberrations	Not tested	+	Zura and Grant 1981
<i>Sphaerechinus granularis</i> <i>Parachetrotus lividus</i> (sea urchins)	Chromosomal aberrations	Not tested	+	Cipollaro et al. 1986
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Morita et al. 1989

– = negative result; + = positive result

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exposure levels and insufficient control of confounding factors. However, the association could not be explained by chance or study deficiencies alone, and an apparent dose response relationship was observed in some studies. Because of study limitations and the lack of a biologically plausible mechanism, it was concluded that there is insufficient evidence to establish a causal relationship between sulfuric acid exposure and laryngeal cancer. There is no information that exposure to sulfuric acid by itself is carcinogenic, and there are no clear data on exposure concentrations of sulfuric acid associated with cancer in humans. The U.S. DHHS (1994) and EPA have not classified sulfur trioxide or sulfuric acid for carcinogenic effects. Based on the human data, which associate occupational exposure to inorganic acid mists containing sulfuric acid with the development of lung and laryngeal cancers, IARC (1992) considers occupational exposure to strong inorganic acid mists containing sulfuric acid carcinogenic to humans (Group 1). Environmental exposure of humans to sulfuric acid has not been associated with cancer (Abbey et al. 1995). The carcinogenicity of sulfuric acid has not been studied in animals after exposure by any route.

Environmental concentrations of sulfuric acid are generally much lower than those found in occupational settings and are unlikely to result in respiratory tract cancers.

**2.6 CHILDREN'S SUSCEPTIBILITY**

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate due to maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or

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function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Foman et al 1982; Owen and Brozek 1966; Ahman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell, BP and Waites GMH 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults and sometimes unique enzymes may exist at particular developmental stages (Leeder and Keams 1997; Komori 1990; Vieira et al 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

The lowest sulfuric acid concentration to produce a respiratory effect was noted in a study of 22 asthmatic adolescents (age 12-19) (Hanley et al. 1992). A transient decrease in FVC and FEV<sub>1</sub> was noted following exposure to 0.07 mg/ m<sup>3</sup> sulfuric acid (MMAD 0.71 μm) while subjects exercised for 10-30 minutes of the 40-45 minute exposure period. No significant changes in respiratory function were noted in asthmatic adolescents (age 13-18) who were exposed to 0.07 mg/ m<sup>3</sup> sulfuric acid (MMAD 0.6 μm) for 90 minutes with alternating periods of rest and exercise (Koenig et al. 1992). In another study, increased respiratory resistance, decreased maximum flow at 50% and 75% of vital capacity, and decreased FEV<sub>1</sub> were observed in

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10 asthmatic adolescents (age 14-18) who were exposed to  $0.1 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.6 \text{ }\mu\text{m}$ ) through a mouthpiece or face mask while exercising for 20 minutes of the 50 minute exposure period (Koenig et al. 1985). In a comparison of results obtained in their studies of asthmatic adolescents and asthmatic seniors, it was concluded by Koenig et al. (1993) that responses differ between the two age groups. Asthmatic seniors (aged 65-75 years) experienced no statistically significant changes in lung function following exposure to  $0.07 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.6 \text{ }\mu\text{m}$ ) during 30 minutes of rest and 10 minutes of exercise (Koenig et al. 1993). Increased mean levels of oral ammonia in seniors (600 ppb) compared to asthmatic adolescents (317-334 ppb) was discussed as a possible reason for the decreased response in seniors (Hanley et al. 1992; Koenig et al. 1993).

A possible mechanism for increased sensitivity in asthmatic children is limited buffering capacity of hydrogen ions due to lower mucous pH in airways (Holma 1985). Increased susceptibility in infants is also possible due to incomplete development of the mucosa and mucous during the first few months after birth (Holma 1985; Reid 1974).

Experiments in 9 atopic adolescents have demonstrated that exposure to 0.1 ppm sulfur dioxide in combination with  $0.068 \text{ mg/m}^3$  sulfuric acid (MMAD  $0.6 \text{ }\mu\text{m}$ )s while exercising for 10 minutes of a 40 minute exposure period, resulted in no additional decrease in  $\text{FEV}_1$ , which was observed following exposure to sulfuric acid alone (6% decrease,  $p < 0.05$ ) (Koenig et al. 1989). Exposure to each individual compound did not result in a statistically significant increase in total respiratory resistance, but a statistically significant 15% increase in total respiratory resistance was observed following exposure to the mixture of compounds. Therefore, sulfur dioxide may potentiate some sulfuric acid-induced effects.

In Uniontown, PA a 2.5 L/min decrease in evening peak expiratory flow rate (PEFR) was observed in 60 asthmatic children (in grades 4 and 5) following 12 hour exposures (weighted for time spent outdoors) to each  $125 \text{ nmo/m}^3$  ( $0.012 \text{ mg/m}^3$  sulfuric acid) increase in particle-strong acidity (extractable acidity from sulfate particles composed partially of sulfuric acid and ammonium bisulfate) (Neas et al. 1995). Incidence of cough in healthy and asthmatic children was also associated with particle-strong acidity levels. However, air pollution studies are difficult to interpret because of confounding effects from numerous air pollutants. Respiratory function parameters were not affected in 41 children aged 9-12 years (15 healthy, 26 asthmatic or atopic) who were exposed for 4 hours in a chamber to a pollution mixture designed to simulate that of the Uniontown study (Linn et al. 1997). With the exception of ozone, exposure to air pollutants (sulfuric acid MMAD= $0.6 \text{ }\mu\text{m}$  and sulfur dioxide) were three times the levels of Uniontown so that the total dose in 4 hours

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was equivalent to a 12 hour exposure of the Uniontown pollutant mixture. The ozone level could not be increased because a higher concentration would have resulted in irritation. Chemical differences in the composition of the pollution mixture, differences in time course of exposure, and psychological effects of chamber exposure were all discussed as possible reasons for the discrepancies between the studies.

Increased sensitivity to sulfuric acid has been observed in young guinea pigs. Exposure of 5-12 guinea pigs to sulfuric acid ( $1 \mu\text{m}$ ) for 8 hours resulted in  $\text{LC}_{50}\text{s}$  of  $18 \text{ mg}/\text{m}^3$  in 1-2-month-old animals and  $50 \text{ mg}/\text{m}^3$  in 1.5-year-old animals (Amdur et al. 1952a). Due to similarities in sulfuric acid-induced respiratory responses between guinea pigs and asthmatics, guinea pigs are considered a suitable model for extrapolating test results to asthmatics (Amdur 1989a).

Age-related differences in the distribution of sulfuric acid within the lung have been observed. A model was used to determine total and regional sulfuric acid deposition within the respiratory tract during mouth breathing in subjects aged 7, 22, 47, 98, and 240 months (Martonen and Zhang 1993). No consistent, age-related differences were noted for deposition of sulfuric acid within the alveolar compartment. However, total respiratory deposition was greatest in the 7-, 22-, and 48-month-old children, and decreased monotonically as the lungs matured. The increased deposition resulted from smaller airway diameters of children. Differences between adults and children were more pronounced with increased breathing rate, which can occur during exercise. Models were also used to study the deposition of hygroscopic particles in a 48-month-old child under different breathing conditions. Deposition of hygroscopic particles in the 48-month-old child (original diameter  $1 \mu\text{m}$ ) was greatest in the alveolar region during restful breathing but was greatest in the tracheobronchial region during exerted breathing. The models of Martonen and Zhang (1993) suggest increased sensitivity in children, due to increased deposition resulting from smaller airway, and that subject age and breathing parameters need to be addressed in health studies.

Following exposure through any route (e.g., inhalation, oral, dermal, or ocular) it is unlikely that sulfuric acid would reach germ cells, cross the placenta, or be excreted into breast milk. When sulfuric acid contacts tissues, it dissociates into hydrogen and sulfate ions. Hydrogen ions are responsible for the toxic effects, which occur only at the point of contact with sulfuric acid. Studies, which evaluate developmental effects in humans, are not available. However, a limited number of studies in animals have indicated that sulfuric acid is not a developmental hazard (Capdevielle and Scanes 1995a, 1995b; Murray et al. 1979).

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In conclusion, a limited number of studies have suggested that asthmatic adolescents may be more susceptible to transient sulfuric acid-induced changes in respiratory function than asthmatic adults, but more studies are needed before definite conclusions can be made. Increased susceptibility of children may be due to increased pulmonary deposition, as a result of smaller airway diameter (Maronen and Zhang 1993), and limited buffering capacity, resulting from incomplete development of mucous and mucosa (Holma et al. 1985). Additional studies are needed to better characterize susceptibility in children,

**2.7 BIOMARKERS 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 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 sulfur trioxide and sulfuric acid are discussed in Section 2.7.1.

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 (NAWNRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential

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health impairment (e.g., DNA adducts). Biomarkers of effects caused by sulfur trioxide sulfuric acid are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

### **2.7.1 Biomarkers Used to Identify or Quantify Exposure to Sulfur Trioxide/Sulfuric Acid**

There are no established biomarkers of exposure for sulfur trioxide or sulfuric acid. The pH of saliva has been shown to decrease in persons occupationally exposed to sulfuric acid (El-Sadik et al. 1972). The pH of respiratory mucus may also decrease following inhalation exposure to sulfuric acid (Holma 1985). Because many things can affect the pH of saliva and respiratory mucus, a decrease in pH would not be a biomarker unique to sulfuric acid exposure.

### **2.7.2 Biomarkers Used to Characterize Effects Caused by Sulfur Trioxide/Sulfuric Acid**

Changes in pulmonary function tests, observed minutes following acute inhalation exposure of humans to sulfuric acid (Avol et al. 1988; Hanley et al. 1992; Koenig et al. 1985, 1992; Utell et al. 1984), and tooth etching following occupational exposure to sulfuric acid, have been reported (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961). The average exposure duration associated with tooth etching is five years, but etching has also been observed with only three to four months of exposure (Malcolm and Paul 1961). These effects are not unique to sulfuric acid exposure, and clear, concentration-response relationships have not been established for these effects. Because the effects of sulfuric acid exposure are dependent on many factors in addition to concentration, including aerosol size, relative humidity, and breathing factors, a population-based, concentration-response relationship for these effects would be difficult to establish.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990), and for information on biomarkers for neurological effects see OTA (1990).

## 2.8 INTERACTIONS WITH OTHER CHEMICALS

In the environment, sulfuric acid exposure most frequently occurs in combination with exposure to other air pollutants including small metal particles, ozone, sulfur dioxide, and nitrogen oxides. Therefore, there are numerous studies that examine the effects of sulfuric acid in combination with other air pollutants.

Exposure of 19 normal human volunteers to 0.37 ppm ozone, 0.37 ppm sulfur dioxide, and 0.1 mg/m<sup>3</sup> sulfuric acid aerosols (MMAD 0.5 μm) for 2 hours of alternating 15-minute periods of exercise and rest resulted in a 3.7% depression in FEV<sub>1</sub> (Kleinman et al. 1981). The investigators indicated that exposure to ozone alone, under the same conditions, depressed FEV<sub>1</sub> by about 2.8%. A 3-hour exposure to sulfuric acid (0.107 mg/m<sup>3</sup>; MMAD 0.64 μm) 24 hours before a 3-hour exposure to ozone at 0.08, 0.12, or 0.18 ppm significantly enhanced the effect of ozone in asthmatics (Frampton et al. 1995). An ozone concentration-related response was observed for both FVC and FEV<sub>1</sub>, with the effect observed immediately after exposure for FVC, and 4 hours after exposure for FVC and FEV<sub>1</sub>. Significant deficits in lung function were not observed in 30 young (11-18 years old) asthmatics exposed to sulfuric acid (0.127 mg/m<sup>3</sup>; MMAD 0.66 μm), nitrogen dioxide (0.3 ppm), and ozone (0.2 ppm) for 90 minutes (Linn et al. 1995); the subjects exercised during the exposures. Exposure of 9 atopic adolescents (aged 12-18) to a mixture of 0.068 mg/m<sup>3</sup> sulfuric acid (MMAD 0.6 μm) and 0.1 ppm sulfur dioxide by mouth, while exercising for 10 minutes of a 40-minute exposure period, did not result in a further decrease in FEV<sub>1</sub>, which was observed following exposure to sulfuric acid alone (6% decrease, p<0.05) (Koenig et al. 1989). However, exposure to 0.068 mg/m<sup>3</sup> sulfuric acid alone resulted in a nonsignificant, 12% increase in total respiratory resistance, but a significant 15% increase in total respiratory resistance was observed following exposure to the 0.068 mg/m<sup>3</sup> sulfuric acid and 0.1 ppm sulfur dioxide mixture.

Sulfuric acid as a surface layer on aerosols of zinc oxide was more potent in decreasing the diffusing capacity of carbon monoxide in guinea pigs than sulfuric acid aerosol alone (Amdur 1989b). Adsorption of acids to carbon particles may increase toxicity because it restricts neutralization by ammonia in the airways or buffering systems in epithelium (Jakab et al. 1996). Some studies indicate that sulfuric acid potentiates the response to ozone. For example, potentiation of ozone has been observed in rats at sulfuric acid concentrations as low as 40 μg/m<sup>3</sup> (Amdur 1989a). Kimmel et al. (1997) reported a synergistic effect in rats exposed to both sulfuric acid and ozone. The rats were exposed for 4 hours per day, for 2 days, to 0.6 ppm ozone and 0.5 mg/m<sup>3</sup> sulfuric acid with MMDs of 0.3 μm (fine) or 0.06 μm (ultrafine). Exposure to the fine aerosol resulted in significantly increased cell proliferation in the acinar region, an effect not observed with

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the ultrafine aerosol. Exposure to the ultrafine aerosol resulted in an increase in the volume percentage of markedly-to-severely injured tissue, an effect not observed with the fine aerosol. This study indicates that aerosol size also has a role in determining whether or not an interaction between sulfuric acid and other toxicants will occur.

Combined exposure to sulfuric acid and ozone has also been shown to have no potentiating effects compared to exposure to either substance alone. El-Fawal et al. (1995) exposed rabbits nose-only to both ozone (0.1, 0.3, or 0.6 ppm) and sulfuric acid (MMD 0.3  $\mu\text{m}$ ; 50,75, or 125  $\mu\text{g}/\text{m}^3$ ) for 3 hours. After the exposures, sections of bronchi were removed and the responsiveness to acetylcholine was determined in an in vitro assay. The combination of ozone and sulfuric acid reduced the responsiveness to acetylcholine that was observed following ozone exposure alone.

The effects of a 4-hour combined exposure of rats to ozone (0.5 ppm), nitric acid (0.7  $\text{mg}/\text{m}^3$ ), and sulfuric acid (0.6  $\text{mg}/\text{m}^3$ ) were not greater than the effects of a 4-hour ozone exposure (Mautz et al. 1991). Toxicity was assessed through the measurement of breathing patterns, metabolic rates, fatty acid composition of pulmonary surfactant, nasal epithelial injury, oxidant-induced lung parenchymal lesions, and changes in total protein lung in lavage fluid.

Last and Pinkerton exposed rats (6/group) to mixtures of 0.2 ppm ozone and 0.020  $\text{mg}/\text{m}^3$  sulfuric acid (0.4-0.8  $\mu\text{m}$ ) for 12 hours/day, 7 days/week for 30 or 90 days or 0.2 ppm ozone and 0.150  $\text{mg}/\text{m}^3$  sulfuric acid (0.4-0.8  $\mu\text{m}$ ) 23.5 hours/day, 7 days/week for 30 or 90 days. Sulfuric acid did not potentiate an increase in alveolar density, which was observed following exposure to ozone alone (Last and Pinkerton, 1997)

Compared to results in rats exposed to 5 ppm nitrogen dioxide for 1 day, protein in lavage fluid was significantly increased in rats exposed to both 5 ppm nitrogen dioxide and sulfuric acid at 0.5  $\text{mg}/\text{m}^3$  for 1 day (MMAD 0.4  $\mu\text{m}$ ) (Last and Warren 1987). This increased response was not observed after 3 days of exposure. Rats were not exposed to sulfuric acid aerosols alone in this study.

Guinea pigs exposed to sulfuric acid at 8  $\text{mg}/\text{m}^3$  (mean diameter 1  $\mu\text{m}$ ) and sulfur dioxide at 89 ppm for 8 hours showed effects that were more severe than those of exposure to either substance alone (Amdur 1954). Body weight gain, lung pathology, and labored breathing were all more severe following the combined exposure, while the study author noted that exposure to either substance alone at the concentrations used was ineffective in producing a respiratory response.

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To examine the ability of air pollutants to act as a promoter, rats were exposed to nitrogen dioxide (0.4 ppm) and sulfuric acid aerosols (MMAD 0.7  $\mu\text{m}$ ; 1 mg/  $\text{m}^3$ ) for 13 months followed by an 11 -month observation period, with and without pretreatment with a single intraperitoneal injection of N-bis(2-hydroxypropyl) nitrosamine (BHPN; 0.5 g/kg) (Ichinose and Sagai 1992). Nitrogen dioxide exposures were for 24 hours per day, and sulfuric acid aerosol exposures were for 10 hours per day. Treatment with BHPN alone did not result in any tumors, while treatment with nitrogen dioxide and sulfuric acid following BHPN treatment resulted in lung tumors (adenomas and adenocarcinomas) in 3 of 36 rats. This study suggests that the combination of nitrogen dioxide and sulfuric acid can act as a lung tumor promoter.

There is evidence of a possible synergistic relationship between sulfuric acid and smoking in the development of laryngeal cancer. A case control study was conducted of 352 white males with laryngeal cancer and 1050 white male controls. The risk of developing laryngeal cancer was significantly greater in heavy smokers with occupational exposures to sulfuric acid than in heavy smokers with no sulfuric acid exposure. Relative risks for the low (<20 years) and high (>20 years) sulfuric acid exposure categories were 2.05 and 2.43, respectively (Cookfair et al. 1985). The study is limited because actual exposure concentrations were not known.

The relationship between smoking and laryngeal cancer appears to be associated primarily with cigarette smoking. Although an excess risk of laryngeal cancer has been reported among pipe and cigar smokers, pipe and cigar smoke were not found to be confounding factors in a study of laryngeal cancer among workers exposed to sulfuric acid mists (Steenland et al. 1988).

### 2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to sulfur trioxide and sulfuric acid than will most persons exposed to the same level of sulfur trioxide and sulfuric acid in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of sulfur trioxide and sulfuric acid or compromised function of target organs affected by sulfur trioxide and sulfuric acid.

Populations who are at greater risk due to their unusually high exposure to sulfur trioxide and sulfuric acid are discussed in Section 5.7, Populations With Potentially High Exposure.

Asthmatics are more sensitive to sulfuric acid exposure. One reason for their enhanced sensitivity is that the pH of their mucus mass is lower (5.3-7.6) than in normal subjects (7.4-8.2). Thus ofcan neydrogen ions before the pH of the mucus is changed significantly, resulting

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in pH changes in the surrounding tissue. Lowering the pH of mucus increases its viscosity (Holma 1985), which would decrease mucociliary clearance.

Other persons, who have an innately low mucus pH would also be more sensitive to sulfuric acid. The mucus of smokers contains higher levels of lysozyme and total protein, and their mucus may also have a lower capacity to neutralize hydrogen ions (Holma 1989). Because mucus production is not fully developed in infants, they may also be more sensitive to sulfuric acid exposure (Holma 1985; Reid 1974).

In addition to effects on mucus, smokers, and possibly those exposed to second hand smoke, may be at greater risk of the effects of sulfuric acid exposure because mucociliary clearance is already compromised (Albert et al. 1971). Other persons with compromised lung function would also be more sensitive to inhalation exposure to sulfuric acid aerosols. Children are a potentially sensitive subgroup and are discussed under Section 2.6.

## 2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to sulfur trioxide and sulfuric acid. 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 sulfur trioxide and sulfuric acid. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to sulfur trioxide and/or sulfuric acid: Bronstein AC, Currance PL. 1988. *Emergency Care for Hazardous Materials Exposure*; Ellenhorn MJ, Barceloux DG. 1988. *Medical Toxicology*; Gosselin RE, Smith RP, Hodge HC. 1984. *Clinical Toxicology of Commercial Products*; Haddad LM, Winchester H. 1990. *Clinical Management of Poisoning and Drug Overdose*; Stutz DR, Ulin S. 1992. *Hazardous Materials Injuries*.

### 2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to sulfur trioxide or sulfuric acid aerosols can occur by inhalation. Moving the subject to fresh air is the best way to reduce exposure to sulfur trioxide and sulfuric acid aerosols following inhalation exposure.

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Human exposure to sulfuric acid can also occur via ingestion or direct contact with the skin or eyes. After ingestion, emesis should not be induced (Ellenhorn and Barceloux 1988), although gastric suction has been recommended (Haddad and Winchester 1990). Dilution with cold water or milk or neutralization with antacids are recommended only if the acid is not concentrated (Gosselin et al. 1984). If the acid is concentrated, dilution will produce considerable heat which may cause further damage to the gastrointestinal tract (Haddad and Winchester 1990). Following direct contact with the skin or eyes, the affected area should be irrigated continuously with water to help alleviate the increase in temperature (Gosselin et al. 1984). Continuous irrigation with saline has also been recommended (Ellenhorn and Barceloux 1988). Dilution of concentrated sulfuric acid with saline may produce less heat than dilution with water.

### **2.10.2 Reducing Body Burden**

Sulfur trioxide and sulfuric acid are direct-acting toxicants that do not need to be absorbed into the bloodstream to result in adverse effects. Methods for reducing body burden are not applicable for these direct-acting substances. Preventing sulfuric acid from contacting tissues will prevent the adverse effects of sulfuric acid.

### **2.10.3 Interfering with the Mechanism of Action for Toxic Effects**

Because sulfuric acid acts directly on tissues by changing pH, preventing this pH change by dilution or neutralization would reduce or prevent the effects of sulfuric acid. As discussed in Section 2.10.1, dilution must be used with caution if concentrated sulfuric acid is ingested because the heat that is produced could produce additional damage (Haddad and Winchester 1990).

## **2.11 ADEQUACY OF THE DATABASE**

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of sulfur trioxide and sulfuric acid 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 sulfur trioxide and sulfuric acid.

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

**2.11.1 Existing Information on Health Effects of Sulfur Trioxide and Sulfuric Acid**

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to sulfur trioxide and sulfuric acid are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of sulfuric acid. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Because sulfur trioxide reacts with water to form sulfuric acid, studies of the health effects of sulfuric acid are applicable to sulfur trioxide. Therefore, a separate figure for the limited studies of sulfur trioxide is not presented.

**2.11.2 Identification of Data Needs**

On contact with water, sulfur trioxide forms sulfuric acid. Therefore, exposure to sulfur trioxide results in effects that are the same as observed following exposure to sulfuric acid. The following discussion on data needs focuses on studies of sulfuric acid. Separate studies of the effects of sulfur trioxide are not needed.

**Acute-Duration Exposure.** Sulfuric acid is a direct-acting toxicant, resulting in effects in the tissues with which it comes into contact. There are numerous acute-duration inhalation studies regarding the respiratory effects of sulfuric acid in both asthmatic (Anderson et al. 1992; Aris et al. 1991; Avol et al. 1988, 1990; Fine et al. 1987; Frampton et al. 1995; Hanley et al. 1992; Koenig et al. 1985, 1992, 1993; Linn et al. 1986, 1994; Utell et al. 1983, 1989) and healthy volunteers (Amdur et al. 1952b; Anderson et al. 1992; Avol et al.

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**FIGURE 2-4. Existing Information on Health Effects of Sulfuric Acid**

		SYSTEMIC									
		Death	Acute	Intermediate	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation		•	•		•	•	•				•
Oral		•	•								
Dermal		•	•								

**Human**

		SYSTEMIC									
		Death	Acute	Intermediate	Chronic	Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
Inhalation		•	•	•	•	•	•	•	•		
Oral		•	•	•				•	•		
Dermal			•								

**Animal**

• Existing Studies

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1988; Bowes et al. 1995; Culp et al. 1995; Frampton et al. 1992, 1995; Gamble et al. 1984a; Horvath et al. 1987; Knapp et al. 1991; Kulle et al. 1982; Laube et al. 1993; Leikauf et al. 1981, 1984; Linn et al. 1994; Newhouse et al. 1978; Sim and Battle 1957; Spektor et al. 1989; Stacy et al. 1983; Utell et al. 1984). These studies indicate that asthmatics are more sensitive to respiratory effects following sulfuric acid exposure than healthy subjects. These studies also indicate that aerosol size; relative humidity; and subject factors, including breathing rate and depth, method of breathing (e.g., oral, nasal, oronasal), and respiratory tract ammonia, all influence the response to inhalation of sulfuric acid aerosols. A study in healthy asthmatics demonstrated changes in pulmonary function at a sulfuric acid concentration of  $0.45 \text{ mg/ m}^3$ , but not  $0.1 \text{ mg/ m}^3$  (Utell et al. 1983).

Accidental acute oral exposure of humans to concentrated sulfuric acid indicates that it is highly corrosive to the gastrointestinal tract (Aktug et al. 1995; Dilawari et al. 1984). Dermal corrosions result when the skin of humans comes into contact with sulfuric acid of sufficient concentration (Branday et al. 1996; Schultz et al. 1968). In an experimental study, no skin effects were observed when 10% sulfuric acid was placed on the skin of volunteers (Nixon et al. 1975).

There are numerous acute-duration inhalation studies in animals regarding the respiratory effects of sulfuric acid (Amdur 1958,1959; Amdur et al. 1952a, 1978; Cavender et al. 1977; Chen et al. 1992a, 1992b; Cockrell et al. 1978; El-Fawal and Schlesinger 1994; Grose et al. 1982; Kobayashi and Shinozaki 1993; Lee et al. 1995; Mannix et al. 1991; Schlesinger 1990a; Schlesinger and Gearhart 1986; Schlesinger et al. 1984, 1990b; Stengel et al. 1993; Warren and Last 1987; Wolff et al. 1979; Zelikoff and Schlesinger 1992; Zelikoff et al. 1994). These studies indicate that guinea pigs are the most sensitive species and that the measurement of mucociliary clearance of tracer particles is a more sensitive technique than pulmonary function tests. Studies in animals also indicate that the effects of inhalation of sulfuric acid aerosols are dependent on aerosol size. Acute-duration oral studies concerning the concentration of sulfuric acid required to cause gastrointestinal tract effects were not identified. A 14-day study of chicks fed sulfuric acid in the diet revealed that this route of exposure to sulfuric acid was relatively well tolerated (Capdevielle and Scanes 1995b). Acute-duration dermal studies of sulfuric acid do not agree on the concentration that results in dermal effects. One study reported erosion of the skin at 10% with no effects at 2.5% (Sekizawa et al. 1994), while another study reported no dermal effects at 10% (Nixon et al. 1975). Following direct application of sulfuric acid to the eyes of animals, one study reported severe corneal opacities at 10% with minimal effects at 5% (Murphy et al. 1982), while a second study reported no effects at 10% (Jacobs 1992).

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Although there are numerous acute-duration inhalation studies of sulfuric acid in both humans and animals, an acute-duration MRL was not derived. An MRL was not derived because the methodology for derivation does not incorporate all the variables in addition to concentration that determine the response to sulfuric acid. Rather than additional acute-duration inhalation studies, more work regarding methodology for developing MRLs for hygroscopic aerosols and acute inhalation irritants is needed. Further development of models that examine the effect of aerosol size on the deposition of sulfuric acid aerosols in the lungs (Martonen and Patel 1981; Martonen and Zhang 1993) would also be useful for development of an acute-duration inhalation MRL. Data are not sufficient for the development of an acute-duration oral MRL for sulfuric acid. Additional studies to determine the concentration of sulfuric acid that can be tolerated by the gastrointestinal tract would be of value to poison control centers. Additional dermal and ocular studies that clarify the threshold sulfuric acid concentration resulting in skin and eye irritation are needed.

**Intermediate-Duration Exposure.** There are no intermediate-duration inhalation, oral, or dermal studies of sulfuric acid in humans. Respiratory effects have been studied in animals following intermediate-duration inhalation exposure. The focus of these studies has been histopathological changes in the respiratory tract (Cavender et al. 1977; Thomas et al. 1958) and clearance of test particles (Schlesinger and Gearhart 1986; Schlesinger et al. 1979, 1992a). The only intermediate-duration oral study is a 15-day study in which no systemic growth (liver, kidney, endocrine) effects were observed in ducklings fed sulfuric acid in the diet (Capdevielle and Scanes 1995a). No intermediate-duration dermal studies in animals were identified.

The data are not sufficient for developing an intermediate-duration inhalation MRL. A study that examines pulmonary function in persons occupationally exposed to sulfuric acid, in which the exposure conditions are well defined (e.g., concentrations, aerosol size, and relative humidity), is needed. This study should examine changes in pulmonary function over time, including intermediate-duration exposure. Data are not sufficient for the development of an intermediate-duration oral MRL for sulfuric acid. Additional acute studies that clarify the threshold sulfuric acid concentration resulting in direct irritation of the gastrointestinal tract, skin, and eyes, should also identify thresholds that would be protective for intermediate-duration exposure.

**Chronic-Duration Exposure and Cancer.** Chronic occupational exposure to sulfuric acid aerosols has been associated with a small decrease in FVC (Gamble et al. 1984b), increased reports of bronchitis (Kitagawa 1984; Williams 1970), increased tooth erosion (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961), and an increase in periodontal pockets (Tuominen 1991). No chronic-duration studies were identified regarding the effects of sulfuric acid in humans following oral or dermal exposure.

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The only animal studies that examine a wide range of systemic effects in addition to respiratory effects (e.g., cardiovascular, hematological, hepatic, renal, body weight) are chronic studies in cynomolgus monkeys (Alarie et al. 1973) and guinea pigs (Alarie et al. 1973, 1975). The effects noted in these studies were histopathological changes in the lungs of monkeys at 4.79 mg/ m<sup>3</sup> (MMD 0.73 μm) and 0.38 mg/ m<sup>3</sup> (MMD 2.15 μm). At a concentration of 2.43 mg/ m<sup>3</sup> (MMD 3.6 μm) histopathological changes were observed in the alveoli as well as the bronchioles in exposed monkeys, and a decrease in arterial oxygen was also observed. No effects, including histopathological changes in the respiratory tract, were observed in guinea pigs who were exposed to a maximum concentration of 0.9 mg/m<sup>3</sup> (MMD 0.49 μm) (Alarie et al. 1975). Although these studies clearly report effects that were treatment-related, data for end points that did not show treatment-related effects, for example liver enzyme data, were not reported. Increased bronchial sensitivity to acetylcholine (Gearhart and Schlesinger 1986) and decreased clearance of test particles (Gearhart and Schlesinger 1989; Schlesinger et al. 1992a) were reported following a 1 -year exposure of rabbits to sulfuric acid aerosols. No chronic-duration studies were identified regarding the effects of sulfuric acid in animals following oral or dermal exposure.

The data are not sufficient for developing a chronic-duration inhalation MRL. A study that examines pulmonary function in persons occupationally exposed to sulfuric acid for chronic durations, in which the exposure conditions are well defined (e.g., concentrations, aerosol size, relative humidity), is needed. This study should examine changes in pulmonary function over time and should include chronic-duration exposure. Data are not sufficient for the development of a chronic-duration oral MRL for sulfuric acid. Additional studies that clarify the threshold sulfuric acid concentration resulting in direct irritation of the gastrointestinal tract, skin, and eyes, should also identify thresholds that would be protective for chronic-duration exposure.

Occupational exposure to mineral acid aerosols containing sulfuric acid has been associated with the development of respiratory tract cancers, especially laryngeal and lung cancers (Alderson and Rattan 1980; Beaumont et al. 1987; Coggon et al. 1996; Cookfair et al. 1985; Forastiere et al. 1987; Houghton and White 1994; Soskolne et al. 1982, 1984,1992; Steenland and Beaumont 1989; Steenland et al. 1988). However, most of the cancers were in smokers who were also exposed to other chemicals. There is no information that exposure to sulfuric acid by itself is carcinogenic, and there are no clear data on exposure concentrations of sulfuric acid associated with cancer in humans. Environmental exposure of humans to sulfuric acid has not been associated with cancer (Abbey et al. 1995). The carcinogenicity of sulfuric acid alone has not been studied in animals after exposure by any route. Combined sulfuric acid and nitrogen dioxide exposure has

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been shown to act as a promoter of lung tumors in rats (Ichinose and Sagai 1992). Based on the limited human data, which associate occupational exposure to sulfuric acid aerosols with the development of lung and laryngeal cancers, IARC (1992) considers occupational exposure to strong-inorganic-acid mists containing sulfuric acid carcinogenic to humans (Group 1). The DHHS (1994) and EPA have not classified sulfuric acid for carcinogenic effects. Because repeated irritation of the lungs by sulfuric acid exposure is likely to act as a promoter, and because sulfuric acid exposure generally occurs in the presence of other pollutants, further research on the ability of sulfuric acid aerosols to act as a promoter is needed. The carcinogenicity of sulfuric acid has not been studied after exposure by any other route. Because chronic-duration oral and dermal exposure to irritating concentrations of sulfuric acid is unlikely, cancer studies following exposure by these routes are not needed.

**Genotoxicity.** *In vivo* studies regarding the genotoxicity of sulfuric acid were not identified. Sulfuric acid did not increase gene mutation in bacteria (Cipollaro et al. 1986; Demerec et al. 1951). Increases in chromosomal aberrations were observed in root meristematic tissue of the plant *Vicia faba* (Zura and Grant 1981), in Chinese hamster ovary cells (Morita et al. 1989), and in sea urchins (Cipollaro et al. 1986) exposed to sulfuric acid. Other *in vitro* studies in which pH was adjusted with other acids indicate that acidic pH is genotoxic, resulting in chromosomal anomalies in human lymphocytes (Shimada and Ingalls 1975) and mouse lymphoma cells (Cifone et al. 1987) and a transformed-like morphology in Syrian hamster cells (LeBoeuf and Kerckaert 1986). Further studies regarding the mechanism of genotoxic effects following exposure to low pH are needed to determine if mutations induced by low pH is a mechanism in the development of laryngeal cancer.

**Reproductive Toxicity.** Reproductive effects following exposure to sulfuric acid by any route have not been studied in humans. No significant effects on the mean numbers of implants/dam or resorptions/litter were noted in mice or rabbits exposed by inhalation to sulfuric acid aerosols during gestation (Murray et al. 1979). Changes in testes weight were not observed in chicks (Capdevielle and Scanes 1995b) or ducklings (Capdevielle and Scanes 1995a) fed sulfuric acid in the diet. No additional studies were identified regarding reproductive effects of sulfuric acid in animals following exposure by any route. Because sulfuric acid is a direct-acting toxicant, and because it is unlikely to reach reproductive organs, reproductive effects in mammals are not likely following exposure to sulfuric acid by any route. Therefore, additional reproductive studies are not needed at this time.

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**Developmental Toxicity.** The developmental effects of sulfuric acid have not been studied in humans by any route of exposure. No significant effects were observed on fetal body weights or on the incidence of major or minor malformations in mice or rabbits exposed by inhalation to sulfuric acid aerosols during gestation (Murray et al. 1979). Because sulfuric acid is a direct-acting toxicant, and because it is unlikely to reach developing mammals, developmental effects in mammals are not likely following exposure to sulfuric acid by any route. Therefore, additional developmental toxicity studies of sulfuric acid are not needed at this time.

**Immunotoxicity.** The function of alveolar macrophages collected from humans following inhalation exposure to sulfuric acid aerosols for 2 hours was not affected (Frampton et al. 1992). Immunological effects have not been studied in humans following exposure by other routes. Alveolar macrophage function has been shown to be affected in animals following inhalation exposure to sulfuric acid aerosols (Chen et al. 1992a, 1995; Schlesinger et al. 1992b; Zelikoff and Schlesinger 1992). The effects on alveolar macrophage function were not concentration related. Once a critical level of sulfuric acid was reached, no further effects were observed. Effects were greater following exposure to smaller sized aerosols (MMD 0.04  $\mu\text{m}$  versus 0.3  $\mu\text{m}$ ), leading Chen et al. (1992a) to suggest that the smaller droplets deliver a higher dose to the macrophages than the larger droplets. Inhalation exposure to sulfuric acid aerosols has also been shown to enhance antigen-induced histamine release from mast cells collected from exposed guinea pigs (Fujimaki et al. 1992). Mice challenged with *Streptococcus pyrogens* directly after ultrafine sulfuric acid aerosol (2 hours/day for 5 days) exposure did not experience increased mortality (Grose et al. 1982). Additional studies regarding susceptibility of animals to respiratory infections (bacterial, viral) following intermediate- and chronic duration exposure to sulfuric acid exposure are needed.

Immunological and lymphoreticular effects have not been studied following oral or dermal exposure to sulfuric acid. Because sulfuric acid is a direct-acting toxicant, system-wide effects on the immune system are not likely following exposure to sulfuric acid by any route.

**Neurotoxicity.** Fatigue and headaches were reported more frequently in asthmatic volunteers when they were exposed to sulfuric acid aerosols (Avol et al. 1988). In guinea pigs, uncoordinated movement was reported after exposure to 165  $\text{mg}/\text{m}^3$  of sulfuric acid mists but not higher concentrations. Neurological effects have not been studied following oral or dermal exposure of humans or animals. Because sulfuric acid is a direct-acting toxicant, neurological effects other than subjective symptoms associated with irritation and

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pulmonary function changes are not likely following exposure to sulfuric acid by any route. Studies of neurological effects following sulfuric acid exposure are not needed at this time.

**Epidemiological and Human Dosimetry Studies.** Increased mortality, especially of elderly persons and those with preexisting cardiac and respiratory disease, has been reported during or shortly after air pollution episodes (reviewed in Costa and Amdur 1996). In general, increased mortality in these studies correlates more closely with particulate matter, including sulfuric acid aerosols. In a study that tried to distinguish the effects of sulfuric acid aerosols from those of sulfur dioxide and of British smoke (a measure of particulates), the log of sulfuric acid aerosol concentrations in London was most strongly correlated with total mortality than that of sulfur dioxide or British smoke (Thurston et al. 1989). The authors of the study concluded that their study was consistent with the hypothesis that sulfuric acid is the portion of the particulate mass with the greatest health significance. An association between mortality and environmental sulfate concentrations was not observed among 6,340 nonsmokers living in California (Abbey et al. 1995). An increase in asthma symptoms has been associated with increases in environmental sulfate concentrations (Abbey et al. 1993, 1995). Overall mortality of workers was not associated with acid exposure at steel factories (Beaumont et al. 1987) or at a sulfuric acid plant (Englander et al. 1988). Additional studies that examine environmental sulfuric acid concentration and death and respiratory effects in humans would be useful if exposure to other pollutants is taken into consideration.

Occupational exposure to mineral acid aerosols including sulfuric acid has been associated with the development of respiratory tract cancers, especially laryngeal and lung cancers (Alderson and Rattan 1980; Beaumont et al. 1987; Coggon et al. 1996; Forastiere et al. 1987; Houghton and White 1994; Soskolne et al. 1984, 1992; Steenland and Beaumont 1989; Steenland et al. 1988). However, most of the cancers were in smokers who were also exposed to other chemicals. There is no information that exposure to sulfuric acid by itself is carcinogenic, and there are no clear data on exposure concentrations of sulfuric acid associated with cancer in humans. Additional studies of cancer in persons occupationally exposed to sulfuric acid aerosols, especially in a population with detailed exposure information, are needed.

Exposure models for sulfate and hydrogen ions have been developed to provide better predictions of human exposure compared to outdoor air concentrations alone (Suh et al. 1993). When the sulfate model was compared to actual personal exposure data, it was found that sulfate exposure could be adequately predicted by the outdoor concentration, activity of the person, and their use of air conditioning. The hydrogen ion model included a neutralization term and was better at predicting personal exposure when indoor air

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concentrations of hydrogen ion and personal ammonia levels were also included. Because of the importance of personal ammonia levels for predicting hydrogen ion exposure, and because of similar difficulties in measuring personal ammonia and hydrogen ion concentrations, the study authors suggested that direct measurement of personal hydrogen ion exposure may be the only method to accurately determine personal hydrogen ion exposure. Additional studies that examine personal exposure to sulfuric acid are needed to determine the relationship between ambient exposure concentrations and personal exposures.

**Biomarkers of Exposure and Effect**

**Exposure.** There are no established biomarkers of exposure for sulfur trioxide or sulfuric acid. The pH of saliva is decreased in persons occupationally exposed to sulfuric acid (El-Sadik et al. 1972). The pH of respiratory mucus may also decrease following inhalation exposure to sulfuric acid (Holma 198.5). Additional research examining the relationship between sulfuric acid exposure concentration and saliva pH is unlikely to be useful.

**Effect.** Changes in pulmonary function tests following acute inhalation exposure of humans to sulfuric acid (Avol et al. 1988; Hanley et al. 1992; Koenig et al. 1985, 1992; Utell et al. 1984), and tooth etching following occupational exposure to sulfuric acid, have been reported (El-Sadik et al. 1972; Gamble et al. 1984b; Malcolm and Paul 1961). These effects are not unique to sulfuric acid exposure, and clear concentration-response relationships have not been established for these effects. Because the effects of sulfuric acid exposure are dependent on many factors in addition to concentration, including aerosol size, relative humidity, and breathing factors, a population-based concentration-response relationship for these effects would be difficult to establish.

**Absorption, Distribution, Metabolism, and Excretion.** Sulfuric acid inhaled by humans is retained by the lungs (Amdur et al. 1952b). The regional deposition of sulfuric acid in the lungs is determined by aerosol size as well as the method (oral, nasal, oronasal) and rate of breathing (Bowes et al. 1995). The effect of hygroscopic growth within the respiratory tract on the deposition of sulfuric acid aerosols has been modeled in adults (Martonen and Pate1 198 1) and children (Martonen and Zhang 1993). Excess sulfate is excreted in the urine (Vander et al. 1975). Sulfur from instilled sulfuric acid is readily absorbed from the lungs but poorly absorbed from the nose of dogs (Dahl et al. 1983). Additional studies and/or models regarding the deposition of sulfuric acid aerosols in the lungs would be useful. Because sulfuric acid is a

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direct-acting toxicant, additional studies regarding absorption into the bloodstream, distribution within the body, metabolism, and excretion would not provide insight into the toxic effects of sulfuric acid.

**Comparative Toxicokinetics.** Models that compare the deposition of sulfuric acid aerosols in various species were not identified. Additional models that examine the effect of aerosol size and of hygroscopic growth within the respiratory tract are needed to examine the effects of sulfuric acid aerosols in the various species tested.

**Methods for Reducing Toxic Effects.** The toxicity of sulfuric acid can be reduced or prevented if the acid is neutralized or diluted (Gosselin et al. 1984). Further research regarding the best first aid method to dilute sulfuric acid is necessary. Water generates heat; saline or another solution may generate less heat and leave less tissue damage.

**Children's Susceptibility.** Because sulfur trioxide is converted to sulfuric acid upon contact with water, health effects are consistent with those observed with sulfuric acid exposure. Therefore, the discussion on data needs for children will focus on sulfuric acid. Additional data is not required for sulfur trioxide.

A limited number of studies have examined respiratory responses in asthmatic adolescents following exposure to sulfuric acid (Hanley et al. 1992; Koenig et al. 1992, 1985) and it has been suggested that asthmatic adolescents may be more sensitive than asthmatic senior citizens (Koenig et al. 1993). Additional studies which compare sulfuric acid-induced responses in healthy and asthmatic children of various ages to healthy and asthmatic adults would be useful in determining the sensitivity of children.

Models have indicated increased deposition of sulfuric acid within the respiratory tracts of children, especially during periods of exertion (Martonen and Zhang 1993). Additional studies or models which examine distribution of sulfuric acid within the respiratory tract of young versus mature humans or animals would be useful in determining the impact on children's health. Studies which compare deposition of sulfuric acid with different breathing rates would also be useful.

However, studies which examine absorption into the bloodstream, systemic distribution, metabolism, and excretion in immature or pregnant animals would not likely be useful because sulfuric acid is a direct acting toxicant. A lack of developmental effects has been demonstrated in a limited number of studies (Capdevielle and Scanes 1995a, 1995b; Murray et al. 1979) and additional studies are not needed.

Child health data needs relating to exposure are discussed in 5.8.1 Data Needs: Exposures of Children.

### **2.11.3 Ongoing Studies**

Dockery at Harvard University is continuing his research concerning the adverse effects of acid aerosols including sulfuric acid on urban populations (CRISP 1996). Speizer at Harvard University is researching the respiratory health effects of acid air pollutants on children (FEDRIP 1998). His research is a follow-up study of late adolescents living in 15 communities with variable acid aerosol levels in the United States and Canada. Additional ongoing studies regarding the health effects of sulfur trioxide and sulfuric acid were not identified.