3. HEALTH EFFECTS

3.1 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 on the toxicology of hydrogen sulfide. 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.

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

3.2 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 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. LOAELs 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 (LOAELs) or exposure levels 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 and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

There have been numerous case reports of human deaths after acute exposure to presumably high concentrations (≥500 ppm) of hydrogen sulfide gas (Beauchamp et al. 1984). NIOSH (1977a) reported that hydrogen sulfide was the primary occupational cause of unexpected death. Snyder et al. (1995), summarizing 10 years of data (1983–1992) from the Poison Control Centers National Data Collection system, indicated that at least 29 deaths and 5,563 exposures were attributed to hydrogen sulfide during that time period. Most fatal cases associated with hydrogen sulfide exposure occurred in relatively confined spaces, such as sewers (Adelson and Sunshine 1966), animal processing plants (Breysse 1961), waste dumps (Allyn 1931), sludge plants (NIOSH 1985a), tanks and cesspools (Campanya et al. 1989; Freireich 1946; Hagley and South 1983; Morse et al. 1981; Osbern and Crapo 1981), and other closed environments (Deng and Chang 1987; Parra et al. 1991). Almost all individuals described in these reports lost consciousness quickly after inhalation of hydrogen sulfide, sometimes after only one or two breaths (the so-called "slaughterhouse sledgehammer" effect). Many of the case studies involved accidental poisonings for which the concentrations and/or duration of exposure were not known (Allyn 1931; Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Freireich 1946; Hagley and South 1983; Morse et al. 1981). In some cases, the victims were exposed for a period of time ranging from a few minutes to an

hour and were unable to be revived (Adelson and Sunshine 1966; Deng and Chang 1987; NIOSH 1989; Osbern and Crapo 1981).

Death occurring after acute exposure to hydrogen sulfide appears to be the result of respiratory failure or arrest, with most cases initially presenting with respiratory insufficiency, noncardiogenic pulmonary edema, coma, and cyanosis. Three men lost consciousness and died after entering a sewer containing high concentrations of hydrogen sulfide; all had the characteristic odor of hydrogen sulfide at autopsy and presented with cyanosis and pulmonary edema (Adelson and Sunshine 1966). After being exposed to hydrogen sulfide in a bathroom connected to a manure pit, a man developed nausea, vomiting, dizziness, and dyspnea, and died a few hours later; hemorrhagic bronchitis and asphyxiation were noted as the cause of death (Parra et al. 1991).

Estimates of hydrogen sulfide exposure were available for some of the cases reported involving deaths. After developing decerebrate responses to painful stimuli and partial seizures, with subsequent indications of brain stem damage, a 16-year-old boy died (Hagley and South 1983). He was exposed to what was presumed to be hydrogen sulfide in a liquid manure tank; 2 weeks after exposure, hydrogen sulfide concentrations measured 30 cm below the tank manhole were >150 ppm, the detection limit of the equipment. In another incident, a 16-year-old boy was 10 meters away from an underground liquid manure storage tank, the contents of which had been agitating for 30–60 minutes; he began coughing, vomited, lost consciousness, and died (Morse et al. 1981). Autopsy showed tracheobronchial aspiration of stomach contents, focal pulmonary hemorrhages and edema, and small petechial brain hemorrhages. Hydrogen sulfide concentrations were found to be >60 ppm (equipment detection limit) under similar conditions in the vicinity of the accident 2 days later. Although some other gases common to this environment were not detected, it is possible that there was simultaneous exposure to other compounds. A boy and his father were overcome and died after inhaling hydrogen sulfide gas from a discarded drum at a manufacturing dump (Allyn 1931). Although the concentration of the gas inside the drum at the time of exposure was not known, a crude attempt was made to estimate exposure. Gas was collected from the drum 2 weeks after the accident and diluted 1:400 with air. A rat exposed to this dilution died after 40 seconds of exposure.

Three of five men, who lost consciousness within a few minutes of entering a partially drained underground liquid manure storage tank, died before reaching the hospital; autopsy showed that two had massive liquid manure pulmonary aspiration, while the third had fulminant pulmonary edema without manure aspiration (Osbern and Crapo 1981). Markedly elevated heart-blood sulfide-ion levels indicated

significant hydrogen sulfide exposure. Air samples analyzed about a week after the accident detected only 76 ppm of hydrogen sulfide, but the study authors noted that the environmental conditions were probably different (e.g., warmer weather, less-concentrated manure).

Two maintenance workers at an animal tanning company collapsed and died no more than 45 minutes after entering a sewer manhole; a hydrogen sulfide concentration of 200 ppm was obtained just inside the manhole 6 days after the accident (NIOSH 1989). A worker at a poultry feather processing plant died after being exposed to hydrogen sulfide gas for an estimated 15–20 minutes (Breysse 1961). Testing performed later in the area where the exposure occurred indicated that hydrogen sulfide concentrations ranged from 2,000 to 4,000 ppm. Pulmonary, intracranial, and cerebral edema and cyanosis were noted at autopsy.

Claims for acute hydrogen sulfide exposure that occurred over a 5-year period (1969–1973) in Alberta, Canada, primarily among petrochemical workers, were reviewed by Burnett et al. (1977). Acute effects noted included coma, disequilibrium, and respiratory insufficiency with pulmonary edema. Of 221 cases, there were 14 deaths. A follow-up study of 250 workers' claims for hydrogen sulfide exposure from 1979 to 1983 in Alberta, Canada, found 7 fatalities that usually involved the central nervous and respiratory systems; hepatic congestion and cardiac petechiae were also noted (Arnold et al. 1985). The difference in fatality rate (6% down to 2.8%) was attributed to improved first aid training and an increased awareness of the dangers of hydrogen sulfide.

Only very limited information is available on mortality in humans associated with chronic exposure to hydrogen sulfide. Bates et al. (1997), taking advantage of the fact that the New Zealand city of Rotorua is in a geothermally active area, conducted a retrospective ecological epidemiologic study in which they compared the mortality for selected diseases between residents in Rotorua and the rest of New Zealand. Rotorua uses geothermal energy for industrial and domestic heating purposes. Monitoring during the 1970s found levels of hydrogen sulfide as high as 1 mg/m^3 (710 ppb); the most reliable data provided a median concentration of 20 $\mu g/m^3$ (14 ppb) with 35% of the measurements of 70 $\mu g/m^3$ (50 ppb), and 10% over 400 $\mu g/m^3$ (284 ppb). Mortality data examined were limited to the main organ systems known to be at risk in hydrogen sulfide exposure (i.e., the nervous, respiratory and cardiovascular/circulatory systems, and birth defects). Among these four mortality categories, only deaths due to diseases of the respiratory system showed a significantly elevated standardized mortality ratio (SMR=1.18; $p<0.001$). Because the population in the Rotorua area has markedly more Maori than in the rest of New Zealand, and because Maori disease and mortality rates are relatively high compared with those of the non-Maori

population, further analysis was carried out with an adjustment for ethnicity. When these data were stratified by sex and ethnicity, female Maoris had an SMR of 1.61 ($p<0.001$). Carrying the analysis to minor groupings of disease, significant increases in SMR were found for rheumatic fever and chronic rheumatic heart disease (SMR=1.51; $p=0.01$), hypertensive disease (SMR=1.61; $p<0.001$), pneumonia and influenza (SMR=1.20; $p=0.008$), and chronic obstructive respiratory disease and allied conditions (SMR=1.20; $p=0.004$). In their analysis of the data, the authors note the numerous issues that can be raised with regard to ecologic studies such as theirs; the two principal issues being confounded by other exposures (e.g., smoking) and by ethnicity misclassification. Despite the fact that the data indicate significant increases in SMRs, the study authors concluded that "no convincing evidence was found in this study of elevated rates of mortality in Rotorua compared with the rest of New Zealand." They caveat this conclusion with three considerations: not all causes of deaths were considered, exposures were inadequately characterized, and ethnicity misclassification could have obscured important causes of mortality.

Studies performed using laboratory animals exposed to high concentrations of hydrogen sulfide gas have yielded results similar to those observed in humans exposed at high levels. Exposure of Sprague-Dawley rats to 1,655 ppm killed all five animals within 3 minutes (Lopez et al. 1989). All male F-344 rats exposed to 500–700 ppm hydrogen sulfide gas for 4 hours died, while no rats died when exposed to concentrations up to 400 ppm under these conditions (Khan et al. 1990; Lopez et al. 1987, 1988a, 1988b). Ten of 10 male Wistar rats died after a 12-minute exposure (mean) to 800 ppm hydrogen sulfide (Beck et al. 1979). Concentrations of 335–587 ppm that cause death in 50% of the animals tested (LC_{50}) have been reported in Sprague-Dawley, F-344, and Long Evans rats exposed to hydrogen sulfide gas for 2–6-hour periods (Prior et al. 1988; Tansy et al. 1981), although there were fewer deaths in approximately the same dose range in another study using F-344 rats (Prior et al. 1990). No mortality was reported when male Wistar rats were exposed to up to 500 ppm hydrogen sulfide for 2 hours (Higuchi and Fukamachi 1977).

No deaths occurred among 30 adult female CB-20 mice exposed to 100 ppm hydrogen sulfide for 2 hours/day for 1 day (Elovaara et al. 1978), nor in 20 adult female NMRI mice exposed for 1–4 days (Savolainen et al. 1980). All six mice exposed to 722 ppm hydrogen sulfide for 50 minutes died, while 1,872 ppm hydrogen sulfide killed a group of six mice in 10 minutes (Smith and Gosselin 1964). Five Japanese white rabbits died within 30 minutes of exposure to 500–1,000 ppm hydrogen sulfide (Kage et al. 1992).

No mortality was noted during 90-day studies in which male and female F-344 or Sprague-Dawley rats were exposed for 6 hours/day, 5 days/week, to up to 80 ppm hydrogen sulfide (CIIT 1983b, 1983c). Similar results were obtained at the same concentrations and conditions in a companion study using $B6C3F_1$ mice; although two high-dose animals were killed *in extremis*, and two control animals were found dead in the cage (CIIT 1983a).

All reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration are recorded in Table 3-1 and plotted in Figure 3-1.

Respiratory Effects. With acute accidental hydrogen sulfide exposure, numerous respiratory effects are observed. Death usually occurs after respiratory distress or arrest from the disruption of oxidative metabolism in the brain. Respiratory distress has also been noted in individuals who survived after acute exposures (Osbern and Crapo 1981; Peters 1981; Spolyar 1951). Other respiratory effects of acute hydrogen sulfide exposure include noncardiogenic pulmonary edema (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Thoman 1969; Tvedt et al. 1991a, 1991b), sore throat, cough (Burnett et al. 1977; Jaakkola et al. 1990), and dyspnea (Arnold et al. 1985; Burnett et al. 1977; Krekel 1964; Osbern and Crapo 1981; Parra et al. 1991; Ravizza et al. 1982; Stine et al. 1976; Thoman 1969). Cyanosis has been reported in a number of case reports and is believed to result from respiratory distress (Arnold et al. 1985; Tvedt et al. 1991a, 1991b). In most studies, exposure concentrations and/or durations were unknown. Among hydrogen sulfide exposure survivors, respiratory symptoms generally subsided within several weeks of exposure, but occasionally persisted for several months or longer (Duong et al. 2001; Parra et al. 1991). Acute exposure to >500 ppm hydrogen sulfide is considered to cause rapid respiratory failure (Beauchamp et al. 1984).

Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for <25 minutes (Spolyar 1951). Bhambhani and associates have conducted a number of studies of young healthy volunteers exposed to hydrogen sulfide via oral inhalation. Male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for >16 minutes after graded exercise that was performed to exhaustion (Bhambhani and Singh 1991). No effects on expired ventilation or maximum power output

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	12 min				800 M (10/10 died)	Beck et al. 1979	
2	Rat (Fischer- 344)	4 hr				500 M (4-6 used; all died)	Khan et al. 1990	
3	Rat (Sprague-Dawley)	3 min				1655 M (5/5 died)	Lopez et al. 1989	
4	Rat (Sprague-Dawley, Fischer-344, Long Evans)	2 hr				587 (LC50)	Prior et al. 1988	
5	Rat (Sprague-Dawley, Fischer-344, Long Evans)	4 hr				501 (LC50)	Prior et al. 1988	
6	Rat (Sprague-Dawley, Fischer-344, Long Evans)	6 hr				335 (LC50)	Prior et al. 1988	
7	Rat (Fischer- 344)	4 hr				375 M (2/12 died)	Prior et al. 1990	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
8	Rat (Sprague-Dawley)	4 hr				444 (LC50)	Tansy et al. 1981	
9	Mouse (CD-1)	50 min				722 F (6/6 died)	Smith and Gosselin 1964	
10	Rabbit (Japanese white)	14-30 min				500 (5/5 died)	Kage et al. 1992	
Systemic								
11	Human	>16 min	Resp	5 M			Bhambhani and Singh 1991	
			Cardio	5 M				
			Metab	2 M	5 M (increased blood lactate during exercise)			
12	Human	15 min	Resp	10			Bhambhani et al. 1996a	
13	Human	30 min	Resp	5			Bhambhani et al. 1994	
			Cardio	5				

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Human	2x 30 min	Musc/skel		5 M (decrease in citrate synthase when exercising at 50% maximum aerobic power)		Bhambhani et al. 1996b	
15	Human	2x30 min	Cardio	10			Bhambhani et al. 1997	
			Metab		10 (increase in blood lactate and decrease in oxygen uptake)			
16	Human	30 min	Resp		2[b] (increased airway resistance and decreased specific airway conductance in 2/10 asthmatics)		Jappinen et al. 1990	
17	Rat (Sprague-Dawley)	3 hr	Resp	80 M	200 M (necrosis of olfactory epithelium and regeneration of respiratory epithelium in nose)		Brenneman et al. 2002	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
18	Rat (Sprague-Dawley)	3 hr 5 d	Resp	30 M	80 M (necrosis of nasal olfactory epithelium in 5/5 rats)		Brenneman et al. 2002	
19	Rat (Fischer- 344)	4 hr	Resp		200 M (increase in protein and lactate dehydrogenase in lavage fluid; focal areas of perivascular edema; proteinaceous material in the alveoli)		Green et al. 1991	
20	Rat (Wistar)	1 hr	Resp		100 M (increased respiration rate)		Higuchi and Fukamachi 1977	
			Cardio		100 M (increased blood pressure, heart rate)			
21	Rat (Fischer- 344)	4 hr	Resp	10 M	50 M (15% reduction in lung cytochrome c oxidase activity)		Khan et al. 1990	
22	Rat (Fischer- 344)	4 hr	Resp	50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
23	Rat (Wistar)	20-60 min	Resp		75 M (slight congestion)		Kohno et al. 1991	
			Cardio			75 M (cardiac arrhythmia; decreased heart rate)		
24	Rat (Fischer- 344)	4 hr	Resp		10 M (increased cellularity in nasal lavage fluid)		Lopez et al. 1987	
25	Rat (Fischer- 344)	4 hr	Resp		83 M (mild perivascular edema)		Lopez et al. 1988a	
26	Rat (Fischer- 344)	4 hr	Resp			400 M (severe inflammation and necrosis of respiratory and olfactory epithelium)	Lopez et al. 1988b	
27	Rat (Fischer- 344)	4 hr	Ocular	200 M	400 M (epiphora)		Lopez et al. 1988b	
28	Rat (Fischer- 344)	4 hr	Resp			375 M (moderate to massive pulmonary edema)	Prior et al. 1990	
29	Gn Pig (NS)	11 d 1 hr/d	Ocular		20 M (eye irritation)		Haider et al. 1980	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
30	Rabbit (mixed breeds)	1.5 hr or 5 d 0.5hr/d	Cardio			72 (changes in ventricular repolarization; cardiac arrhythmia)	Kosmider et al. 1967	
Immuno/ Lymphoret								
31	Rat (Fischer- 344)	4 hr		50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991	
Neurological								
32	Human	30 min			2 (headache in 3/10 asthmatics)		Jappinen et al. 1990	
33	Rat (Wistar)	20 min				800 M (unconsciousness)	Beck et al. 1979	
34	Rat (Wistar)	2 hr		100 M	200 M (decreased response rate in conditioned avoidance task)		Higuchi and Fukamachi 1977	
35	Rat (Fischer- 344)	4 hr		200 M	400 M (lethargy)		Lopez et al. 1988b	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
36	Rat (CD)	3 hr/d 5 d		30 M	80 M (decreased spontaneous motor activity)		Struve et al. 2001	
37	Gn Pig (NS)	11 d 1 hr/d			20 M (decreased cerebral hemisphere and brain stem total lipids and phospholipids)		Haider et al. 1980	
38	Rabbit (mixed breeds)	1.5 hr				72 (unconsciousness)	Kosmider et al. 1967	
INTERMEDIATE EXPOSURE								
Systemic								
39	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 10 wk	Resp	10[c] M	30 M (olfactory neuron loss and basal cell hyperplasia in nasal olfactory epithelium)		Brenneman et al. 2000	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
40	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d	Resp	10	30 (olfactory neuron loss in the nasal olfactory epithelium)		CIIT 1983b	
			Cardio	80				
			Gastro	80				
			Hemato	80				
			Musc/skel	80				
			Hepatic	80				
			Renal	80				
			Endocr	80				
			Dermal	80				
			Ocular	80				
			Bd Wt	80				

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
41	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d	Resp	10	30 (olfactory neuron loss in the nasal olfactory epithelium and bronchiolar epithelial hyperplasia)		CIIT 1983c	
			Cardio	80				
			Gastro	80				
			Hemato	80				
			Musc/skel	80				
			Hepatic	80				
			Renal	80				
			Endocr	80				
			Dermal	80				
			Ocular	80				
			Bd Wt	80 M 30.5 F[d]	80 F (10% decrease in body weight)			
42	Rat (Sprague-Dawley)	gd 1-ppd 21 7 hr/d	Metab		20 F (50% increase in circulating glucose levels in dams)		Hayden et al. 1990a	
43	Rat (Sprague-Dawley)	gd 6-ppd 21 7 hr/d	Hepatic	50 F	75 F (increased maternal liver cholesterol levels)		Hayden et al. 1990b	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
44	Rat (Sprague-Dawley)	gd 6-20 6 hr/d	Bd Wt	100 F	150 F (pregnant rats lost weight)		Saillenfait et al. 1989	
45	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d	Resp	10	30 (olfactory neuron loss in the nasal olfactory epithelium)		CIIT 1983a	
					80 (inflammation of nasal mucosa)			
			Cardio	80				
			Gastro	80				
			Hemato	80				
			Musc/skel	80				
			Hepatic	80				
			Renal	80				
			Endocr	80				
			Dermal	80				
			Ocular	80				
			Bd Wt	30.5	80 (7-14% decrease in body weight)			

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
46	Pig (Crossbred)	17 d 24 hr/d	Resp	8.5			Curtis et al. 1975	
			Gastro	8.5				
			Hepatic	8.5				
			Renal	8.5				
			Ocular	8.5				
			Bd Wt	8.5				
Immuno/ Lymphoret								
47	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		80			CIIT 1983b	
48	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c	
49	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a	
Neurological								
50	Rat (Fischer- 344)	90d 5 d/wk 6 hr/d		80			CIIT 1983b	
51	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		30.5[d] M 80 F	80 M	(5% decrease in brain weight)	CIIT 1983c	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
52	Rat (Sprague-Dawley)	25 wk 5 d/wk		50 M			Gagnaire et al. 1986	
53	Rat (Sprague-Dawley)	4 hours/day 5 days/week 5-11 weeks			125 M (impaired learning of new tasks on a radial arm maze)		Partlo et al. 2001	
54	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a	
Reproductive								
55	Rat (Fischer- 344)	90d 5 d/wk 6 hr/d		80			CIIT 1983b	
56	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c	
57	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000	
58	Mouse (B6C3F1)	90d 5 d/wk 6 hr/d		80			CIIT 1983a	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
Developmental								
59	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000	
60	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d			20 F (severe alterations in architecture and growth characteristics of Purkinje cell dendritic fields which may be indicative of neurotoxicity)		Hannah and Roth 1991	
61	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d		50	75 (decreases in brain amino acid levels of pups)		Hannah et al. 1989, 1990	
62	Rat (Sprague-Dawley)	gd 1-ppd 21 7 hr/d		75 F			Hayden et al. 1990a	
63	Rat (Sprague-Dawley)	gd 6-ppd 21 7 hr/d		75 F			Hayden et al. 1990b	
64	Rat (Sprague-Dawley)	gd 6-20 6 hr/d		150 F			Saillenfait et al. 1989	

Table 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
65	Rat (Sprague-Dawley)	gd 5-ppd 21 7 hr/d			20 F (decreases in norepinephrine in the frontal cortex, increase in serotonin in the frontal cortex of pups)		Skrajny et al. 1992	

a The number corresponds to entries in Figure 3-1.

b Used to derive an acute-duration Minimal Risk Level (MRL) of 0.07 ppm; concentration divided by an uncertainty factor of 27 (3 for use of a minimal LOAEL, 3 for human variability, and 3 for database deficiencies).

c Used to derive an intermediate-duration Minimal Risk Level (MRL) of 0.02 ppm; the NOAEL was adjusted for intermittent exposure and multiplied by the regional gas dose ratio (RGDR) for extrathoracic effects to calculate a human equivalent concentration (HEC). The MRL was obtained by dividing the NOAEL(HEC) by an uncertainty factor of 30 (3 for extrapolation from animals to humans with a dosimetric adjustment and 10 for human variability)

d Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

B = both; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; gd = gestational day; hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; metab = metabolism; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = post-partum day; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation

Acute (≤14 days)

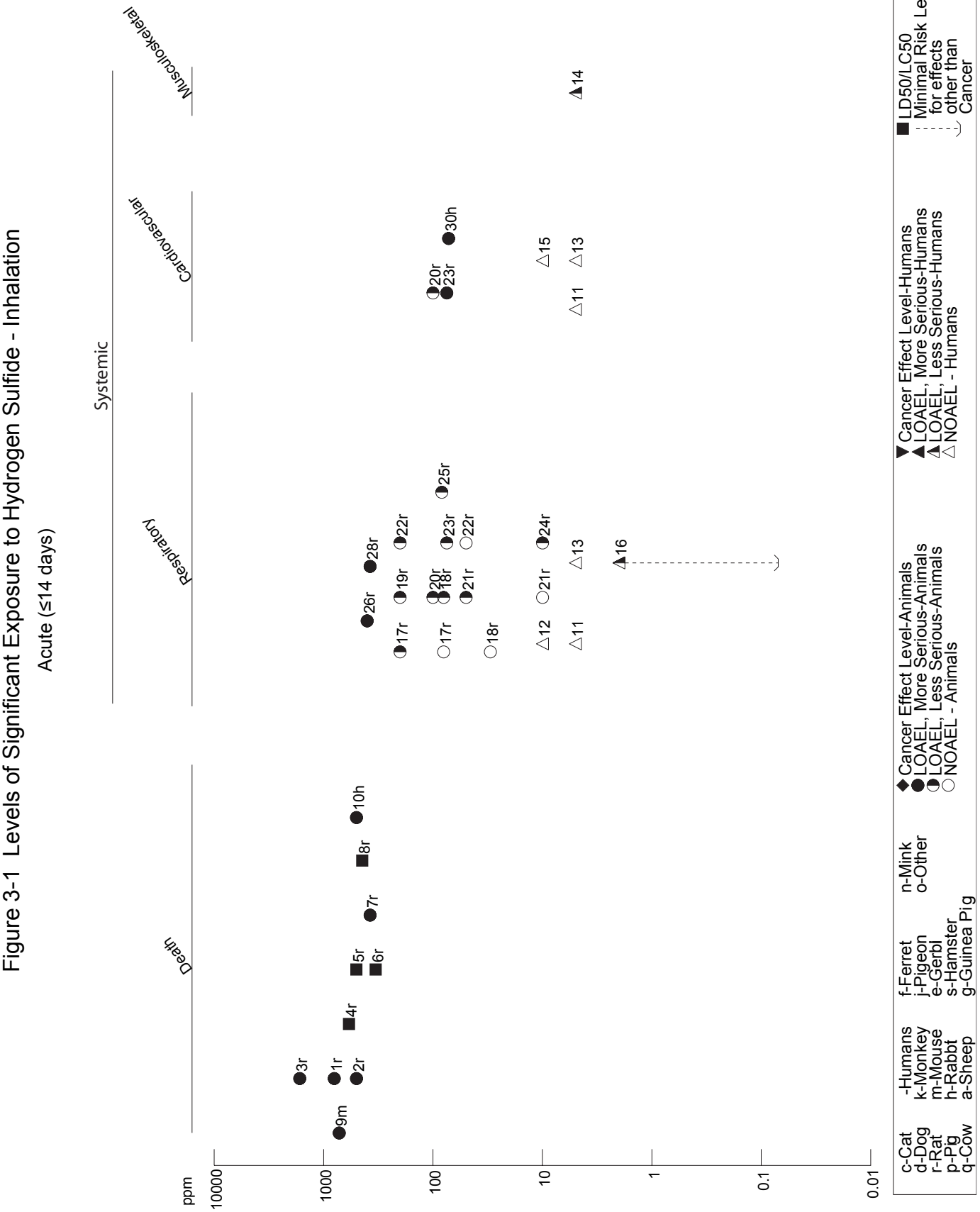
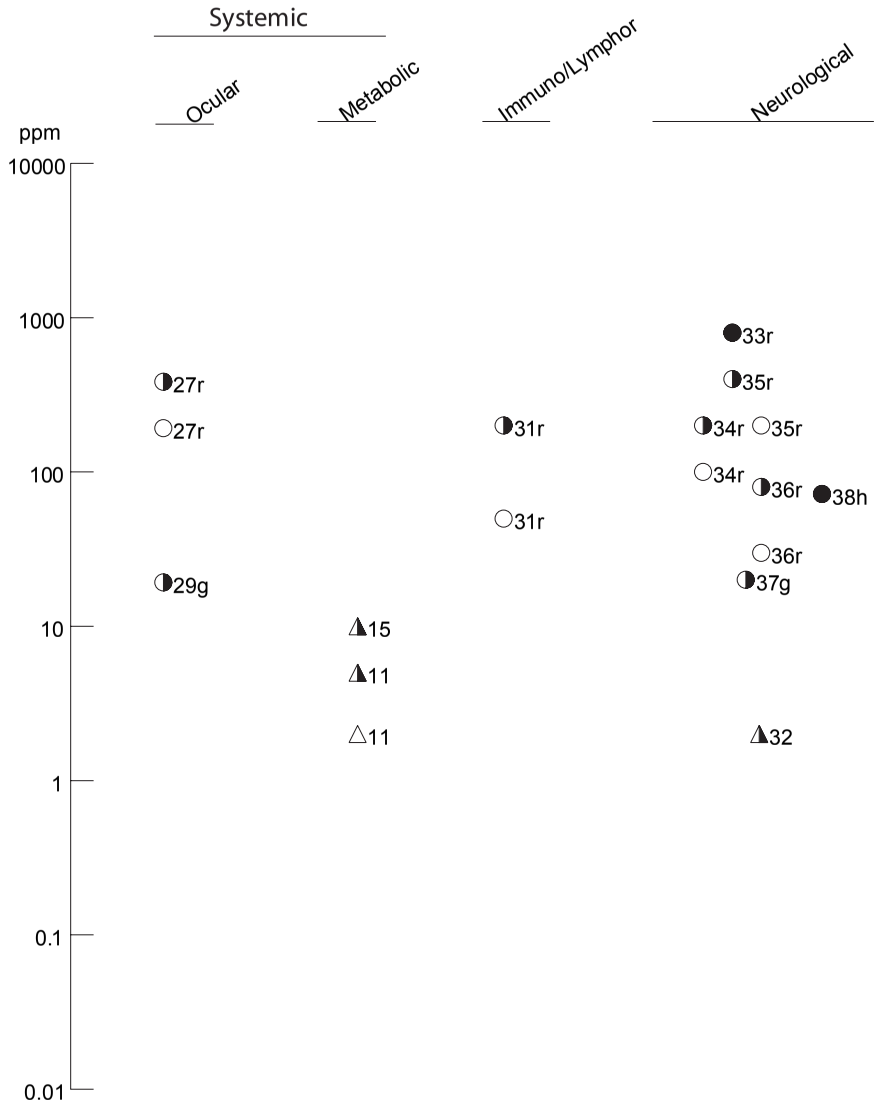


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation (*Continued*)

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(continued)*

Intermediate (15-364 days)

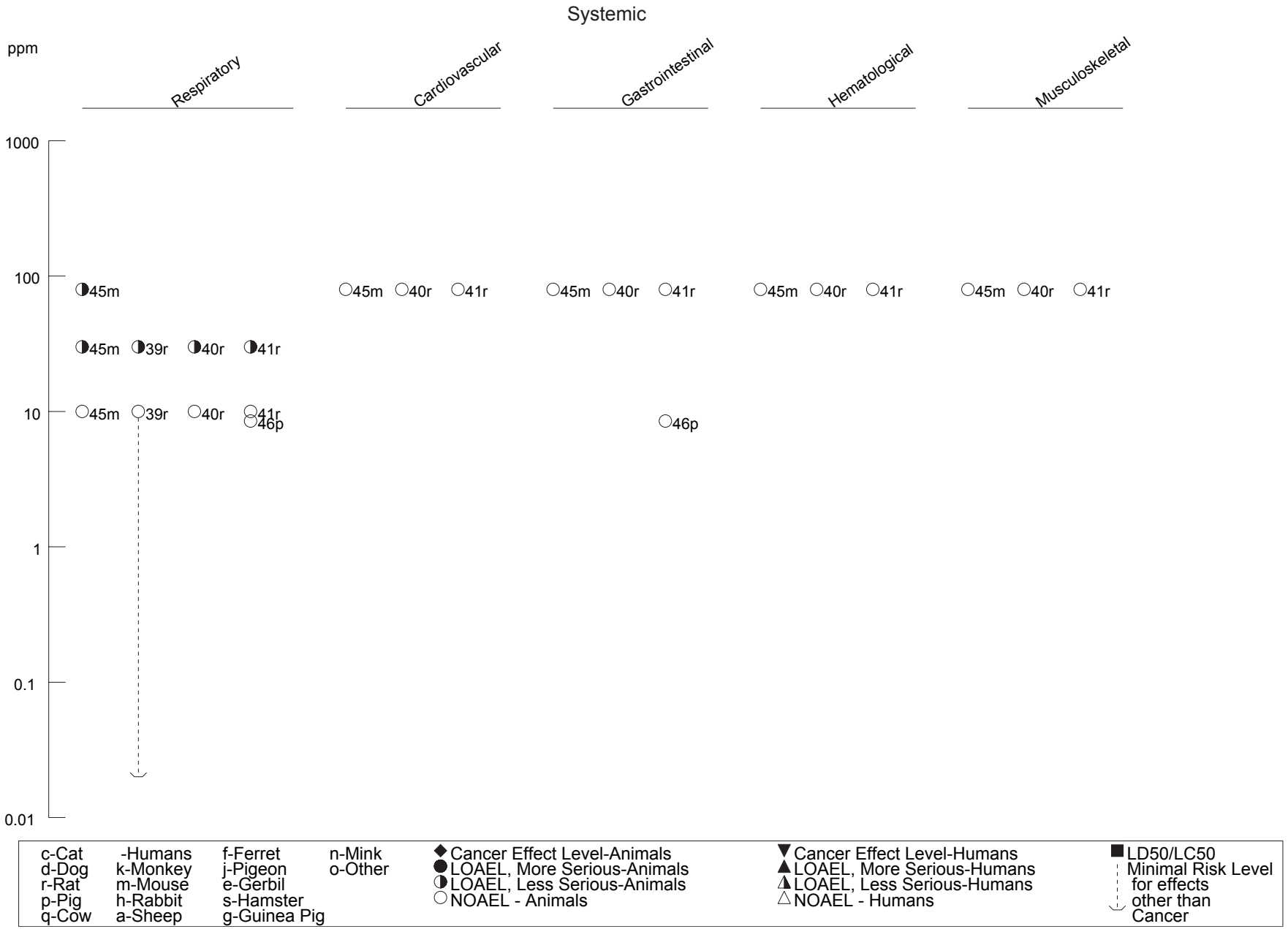


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(continued)*

Intermediate (15-364 days)

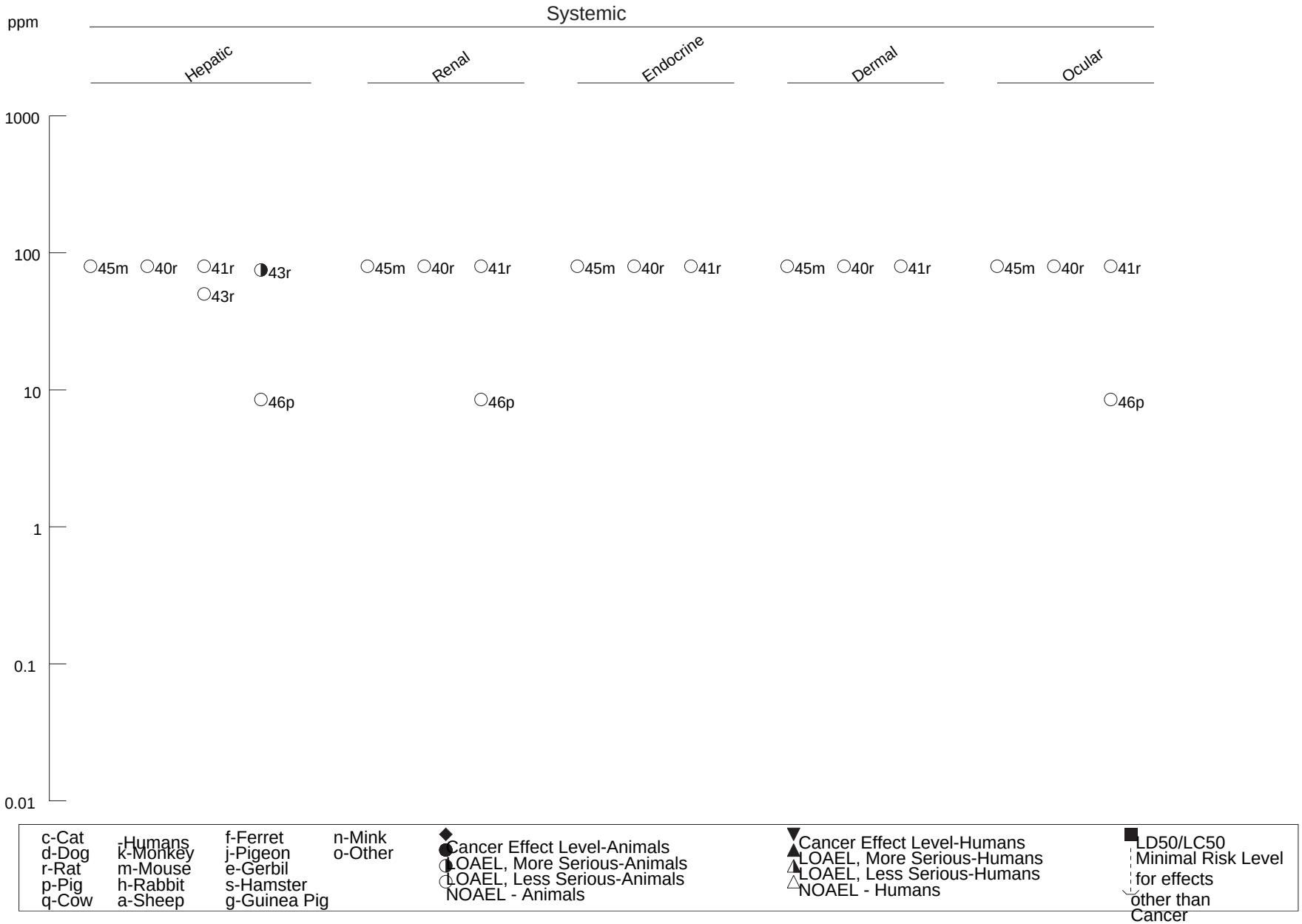
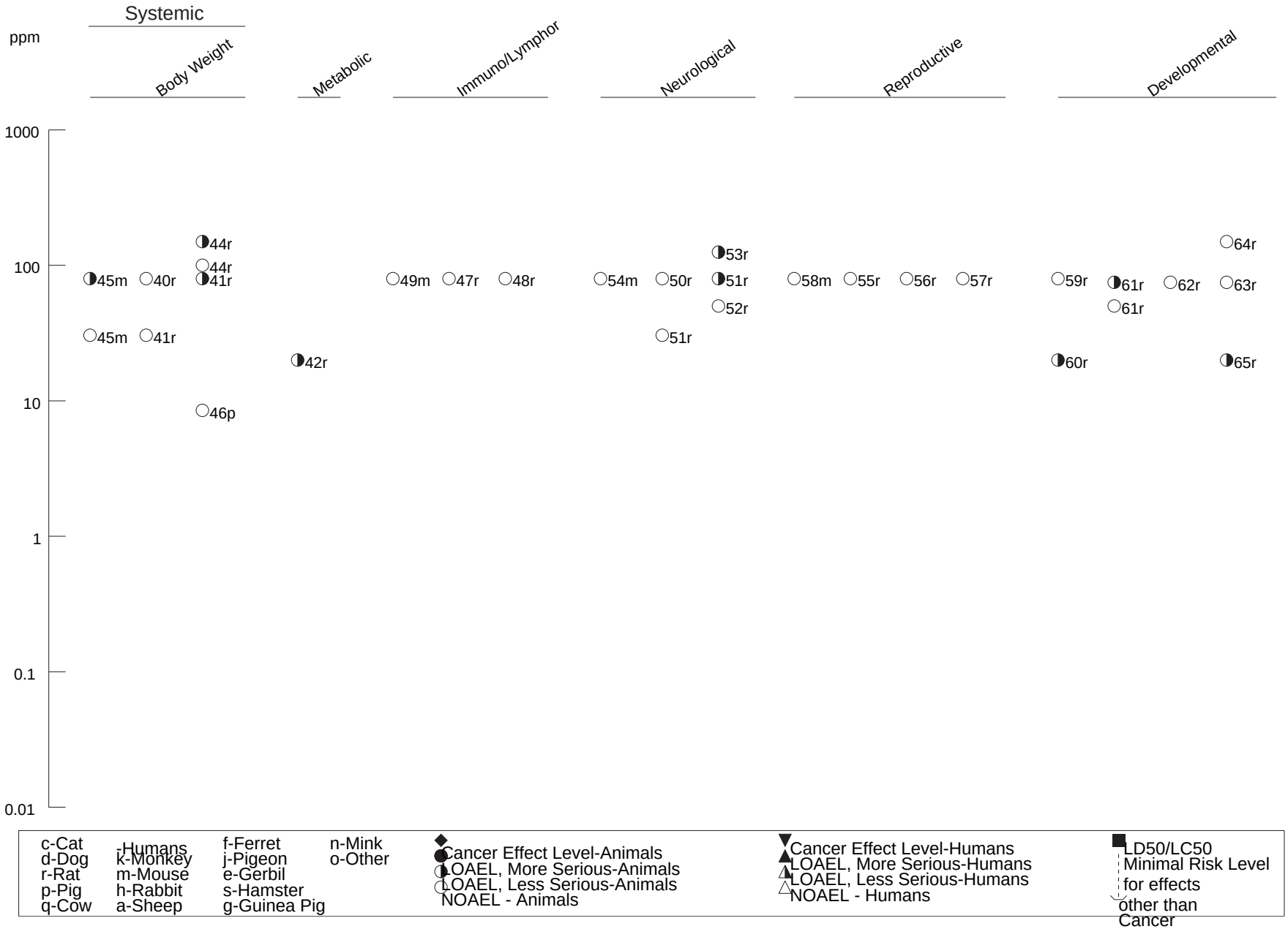


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(continued)*

Intermediate (15-364 days)



were noted, but exposure to 5 ppm resulted in a significant increase in maximum oxygen uptake compared to controls. At exposures to 2 and 5 ppm, the respiratory exchange ratio was decreased significantly compared to controls. The study authors attributed this to a nonsignificant trend toward increased oxygen uptake and decreased carbon dioxide output compared to controls (Bhambhani and Singh 1991). Another study examined the effects of inhalation of 5 ppm hydrogen sulfide on respiratory physiological parameters and found no changes in partial pressure of oxygen, partial pressure of carbon dioxide, oxygen uptake (VO_2), percentage of oxygen uptake (VO_2%), uptake of carbon dioxide (VCO_2) and V_E, or respiratory exchange ratio in male or female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A third study found that inhalation of 10 ppm of hydrogen sulfide for 15 minutes at elevated metabolic and ventilation rates did not result in significantly altered pulmonary function test results in men and women (Bhambhani et al. 1996a). It should be noted that the subjects were unable to smell the hydrogen sulfide and their eyes were not exposed to the gas.

Pulmonary function tests were performed on persons with asthma exposed to 2 ppm of hydrogen sulfide for 30 minutes in a sealed chamber (Jappinen et al. 1990). Although no significant changes were noted in airway resistance or specific airway conductance as a group, 2 of 10 subjects showed changes in excess of 30% in both airway resistance and specific airway conductance, an indication of bronchial obstruction (Jappinen et al. 1990). No statistically significant changes were noted in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory flow (Jappinen et al. 1990). Pulmonary function was unaffected following the same exposure protocol in 26 male pulp mill workers who had previously had daily hydrogen sulfide exposures, usually to <10 ppm (Jappinen et al. 1990). No significant changes were noted in FVC, FEV_1, or bronchial responsiveness to histamine challenge in this group of workers, which included subgroups of smokers, workers with previous allergies, and atopic individuals. Findings in this study are similar to those observed in Bhambhani et al. (1996a).

Hessel et al. (1997) examined the pulmonary health effects of hydrogen sulfide exposure in a group of Canadian oil and gas workers. Exposure to hydrogen sulfide was assessed by questionnaire as was the occurrence of respiratory symptoms; in addition, smoking and occupational histories were conducted. Lung health was assessed via spirometric testing and by skin prick testing for six common antigens. The workers were divided into three exposure groups: none, gas exposure (sufficient to produce symptoms), and knockdown (exposure sufficient to cause unconsciousness). None of the lung function indicators (FEV_1, FVC, or FEV_1/FVC) differed significantly among the three groups. Significantly increased odds ratios (ORs) were seen only in those in the knockdown group who showed significant excesses for several symptoms, including: shortness of breath (OR=3.55; 95% confidence interval [CI]=1.02–12.4); wheeze

with chest tightness (OR=5.15; 95% CI=1.29–20.6); and attacks of wheeze (OR=5.08; 95% CI=1.28–20.6).

In a cross-sectional study of sewer and water treatment workers, Richardson (1995) evaluated the association of hydrogen sulfide exposures to reduced lung function using spirometric testing. Job titles were used to categorize sewer workers into high, medium, and low exposure groups; however, there was no quantification of hydrogen sulfide levels. Water treatment workers who were not occupationally exposed to hydrogen sulfide were chosen as a comparison group. Findings included significant differences between spirometric values (FEV_1/FVC) of sewer and water treatment workers across a number of age strata, irrespective of smoking status, although smoking status reduced the impact somewhat. When stratified by presumed exposure to hydrogen sulfide, only those sewer workers with presumed high exposure showed a significant difference from water workers, although a dose-related trend in lung function at both medium and high exposures was observed. In addition, the prevalence OR for obstructive lung disease was 21.0 (95% CI=2.4–237.8) in nonsmoking sewer workers with presumed high hydrogen sulfide exposure when compared to nonsmoking water treatment workers. The prevalence odds ratio for sewer workers who smoke versus water treatment workers who smoke was 1.7 (95% CI=0.2–13.6).

In a report comparing community responses to low-level exposure to a mixture of air pollutants from pulp mills, Jaakkola et al. (1990) reported significant differences in respiratory symptoms between polluted and unpolluted communities. The pollutant mixture associated with the pulp mills included particulates, sulfur dioxide, and a series of 'malodorous sulfur compounds.' Major contributors in the latter mixture include hydrogen sulfide, methyl mercaptan, and methyl sulfides. In this study, the responses of populations from three communities (a nonpolluted community, a moderately polluted community, and a severely polluted community were compared). Initial exposure estimates were derived from dispersion modeling; these estimates were subsequently confirmed with measurements taken from monitoring stations located in the two polluted communities. These measurements indicated that both the mean and the maximum 4-hour concentrations of hydrogen sulfide were higher in the more severely polluted community (4 and 56 $\mu g/m^3$; 2.9 and 40 ppb) than in the moderately polluted one (2 and 22 $\mu g/m^3$; 1.4 and 16 ppb). Particulate measurements made concurrently, and sulfur dioxide measurements made subsequently, showed a similar difference in the concentrations of these two pollutants between the two polluted communities. A cross-sectional, self-administered questionnaire was used to gather data on the occurrence (i.e., often or constantly) of a variety of symptoms and effects during two time periods (the past 4 weeks and the previous 12 months). Respiratory end points evaluated included cough, nasal

symptoms, breathlessness or wheezing, numbers of respiratory infections, history of asthma, and chronic respiratory diseases. The occurrence of nasal symptoms and cough was found to be significantly greater in the subjects living in the two polluted communities when compared to those in the nonpolluted community. Breathlessness or wheezing was also increased, although not to the level of significance. All three of these end points showed a dose-related increase; that is, the greatest occurrence of symptoms occurred in the more highly-polluted community, followed by the less polluted, and then the nonpolluted communities. Because of the mixed exposures, however, the role of hydrogen sulfide in these effects is unclear.

A subsequent report by Marttila et al. (1994b) examined the impact of long-term exposure to the same mixture of malodorous sulfur compounds on children from these same three communities. The findings in children (i.e., nasal symptoms and cough) in the most severely polluted community were similar to those reported above and showed increased risks both for the 4-week and the 12-month intervals, although none of these risks reached statistical significance.

Marttila et al. (1995) also examined the relationship between daily exposure to malodorous sulfur compounds (measured as total reduced sulfur [TRS]) from pulp production and experience of symptoms in a small population living in the vicinity of a pulp mill. The major components of the malodorous sulfur compounds are hydrogen sulfide, methyl mercaptan, and methyl sulfides. This work was initiated due to the observation that an unusually high short-term exposure to malodorous sulfur compounds (maximum 4-hour concentrations of hydrogen sulfide at 135 $\mu g/m^3$ [96 ppb]) led to a considerable increase in the occurrence of ocular, respiratory, and neuropsychological symptoms (Haahtela et al. 1992). During the study period, daily mean TRS concentrations varied from 0 to 82 $\mu g/m^3$, and monthly mean concentrations varied from 3 to 19 $\mu g/m^3$. Following a baseline questionnaire, the study was conducted with six consecutive questionnaires after three predefined levels of exposure to TRS (daily mean <10 $\mu g/m^3$, medium exposure 10–30 $\mu g/m^3$, high exposure >30 $\mu g/m^3$). The study found a dose-related increase in the probability of both nasal (i.e., stuffy or runny nose) and pharyngeal irritation. For nasal symptoms, the probability ratios were 3.13 (95% CI=1.25–7.25) and 8.50 (95% CI=3.19–18.64) for medium and high exposure, respectively. For pharyngeal symptoms, the probability ratios were 2.0 (95% CI=0.92–4.14) and 5.20 (95% CI=1.95–1.99) for the medium and high exposure levels, respectively.

Partti-Pellinen et al. (1996) used a cross-sectional, self-administered questionnaire to assess the eye, respiratory tract, and central nervous system symptoms experienced by adults in a slightly polluted and a reference community. In the polluted community, the mean annual TRS concentrations were 2–3 $\mu g/m^3$,

the 24-hour average concentrations varied between 0 and 56 μg/m^3, and the maximum 1-hour concentration was 155 μg/m^3; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 μg/m^3, the 24-hour average concentrations varied between 0 and 24 μg/m^3, and the maximum 1-hour concentration was 152 μg/m^3. In the reference community, the mean sulfur dioxide level was 1 μg/m^3 and the maximum 1-hour concentration was 30 μg/m^3.

Symptoms evaluated over the previous 4 weeks and previous 12 months included eye irritation, nasal irritation, cough, breathlessness or wheezing, and headache or migraine. After adjusting for age, sex, smoking, history of allergic diseases, education, and marital status, increased odds ratios were seen for all of these symptoms at both time periods. However, significant increases in odds ratios were seen only for headache or migraine in the previous 4 weeks (OR=1.82; 95% CI=1.06–31.5) and in the past 12 months (OR=1.70; 95% CI=1.05–2.73) and cough in the past 12 months (OR=1.64; 95% CI=1.01–2.64). These findings led the authors to conclude that the adverse health effects of TRS occur at lower concentrations than previously reported. However, these findings are also confounded by daily average levels of TRS as high as 56 μg/m^3 and by the presence of sulfur dioxide which, though occurring at the same mean annual concentration in the two communities, showed much higher peaks in the polluted community. Furthermore, no information was provided on particulate levels, which could also be important to these findings.

This series of studies (Jaakkola et al. 1990; Haahtela et al. 1992; Marttila et al. 1994a, 1994b, 1995; Partti-Pellinen et al. 1996) report the results of the South Karelia Air Pollution Study, which began in 1986 to evaluate the effects of air pollution on human health and the environment. In the early studies of this series (Haahtela et al. 1992; Jaakkola et al. 1990; Marttila et al. 1994b), levels of hydrogen sulfide, sulfur dioxide, particulates, and methyl mercaptan were individually reported. In the later studies (Marttila et al. 1994a, 1995; Partti-Pellinen et al. 1996), a complex mixture of ‘malodorous sulfur components’ (that included hydrogen sulfide, methyl mercaptan, and methyl sulfides) was monitored as TRS using a method that first removes any sulfur dioxide, then oxidizes the TRS compounds to sulfur dioxide, and reports the results as μg/m^3 TRS. It is not possible, from the information provided, to determine precisely what proportion of the TRS is actually hydrogen sulfide, although the authors indicate that it is about two-thirds (Marttila et al. 1994b). The fact that in virtually all of these studies, effects were linked to exposures to mixtures, even though hydrogen sulfide appears to have been the dominant sulfur compound, complicates interpretation of these results. It is probably reasonable to conclude that these studies demonstrate that low levels of hydrogen sulfide in combination with other

sulfur-containing pollutants, and possibly due to combination with particulates and/or sulfur dioxide, can have an adverse effect on respiratory health. However, it is not possible at this time to determine whether it is the low annual average values of 1–2 μg/m^3 TRS, or the daily average concentrations (56 μg/m^3 TRS) that are associated with these findings.

ATSDR (Campagna et al. 2004) examined the possible relationship between ambient levels of hydrogen sulfide and total reduced sulfur and hospital visits among residents of Dakota City and South Sioux City, Nebraska. Total reduced sulfur is the combined concentrations of hydrogen sulfide, methyl mercaptan, dimethyl sulfide, and dimethyl disulfide; air monitoring data indicate that hydrogen sulfide was the primary constituent of the total reduced sulfur. The primary sources of total reduced sulfur were a beef slaughter facility and a leather tanning facility. Among children under 18 years of age, positive associations were found between hospital visits for all respiratory disease (including asthma) and the high hydrogen sulfide level the previous day and the high levels of total reduced sulfur on the previous day. Positive associations were found between hospital visits for asthma and the previous day's high hydrogen sulfide level in adults and total reduced sulfur in children. A high total reduced sulfur or hydrogen sulfide level was defined as a 30-minute rolling average of ≥30 ppb.

As discussed in more detail in Section 3.2.1.1, Bates et al. (1997) found a significant increase in mortality from diseases of the respiratory system for residents of the Rotorua area of New Zealand for the period of 1981–1990. Rotorua is in an area of high geothermal activity; sampling from a campaign in 1978 indicated a median concentration for hydrogen sulfide of about 20 μg/m^3 with 35% of the measurements >70 μg/m^3 and 10% of the measurements >400 μg/m^3. Problems with the analysis, however, led these authors to conclude that there were no clear indications of excess mortality. In a follow-up to this study, Bates et al. (2002) used hospital discharge records for 1993–1996 to assess the incidence of respiratory disease; unlike the previous study, exposure was classified as high, medium, or low, based on residence at the time of discharge. A statistically significant ($p<0.001$), exposure-related trend for increased incidence of respiratory disease was found. The incidence of minor respiratory disease groups was also significantly ($p<0.01$) increased. In general, the incidence of respiratory disease was significantly elevated in the high exposure group, but not at lower exposure levels, with the exception of the incidences of other diseases of the upper respiratory tract category, which were increased in all three exposure groups. The standardized incidence ratios (SIRs) (and 95% confidence limits) for this category were 1.48 (1.34–1.63), 1.68 (1.39–2.01), and 1.98 (1.58–2.45) in the low, medium, and high exposure groups, respectively. Limitations in the design of this study, such as lack of exposure monitoring data, lack of data on potential confounding factors (e.g., smoking, differences in socioeconomic status in the different

exposure groups), lack of residence history data, and lack of information on potential exposure at work, limit the interpretation of these data.

In addition to an increase in respiration rate that was noted in Wistar rats exposed to 100–200 ppm hydrogen sulfide for 1 hour (Higuchi and Fukamachi 1977), a number of histological and biochemical changes have been noted in the respiratory tissues and fluids of animals acutely exposed to hydrogen sulfide. Cytotoxicity to both nasal or bronchioalveolar lavage and pulmonary cells was demonstrated in a study of male F-344 rats exposed to 0, 10, 200, or 400 ppm hydrogen sulfide for 4 hours and examined at 1, 20, or 44 hours postexposure (Lopez et al. 1987). Cellularity of nasal lavage fluid was increased at all exposure concentrations, because of either exfoliation of degenerated epithelial cells at 1 hour, or exudation of polymorphonuclear leukocytes (PMNs) at 20 hours postexposure, which served as an indicator of cell damage. Altered pulmonary vascular permeability was indicated by increased protein in nasal lavage fluids in animals exposed to airborne concentrations of 400 ppm, but this condition resolved by 20 hours postexposure. Increased lactate dehydrogenase activity (at exposure levels of 200 and 400 ppm) and alkaline phosphatase activity (with exposure to 400 ppm) in bronchoalveolar lavage fluid observed in this study were indicative of toxic effects on the pulmonary epithelium. In addition, pulmonary alveolar macrophages from animals exposed by inhalation to airborne concentrations of 200 or 400 ppm hydrogen sulfide had some increase in cytoplasmic vacuolation, but the bronchoalveolar epithelium did not show signs of cellular degeneration or ciliocytophthoria (Lopez et al. 1987).

In similar experiments, Green et al. (1991) exposed male F-344 rats to 200 and 300 ppm hydrogen sulfide for 4 hours, and evaluated the impact on lung lavage fluid surface tension, protein concentrations, and lactate dehydrogenase activity. These authors found significant increases in protein concentrations and lactate dehydrogenase activity at both exposure concentrations, but a significant change in the surface tension of lavage fluids only at the high dose. Focal area of perivascular edema and proteinaceous material in the alveoli were also seen in the lungs of the exposed animals.

Histopathological changes have been reported in the nasal cavity of F-344 rats (Lopez et al. 1988b). Male rats were exposed to 0, 10, 200, or 400 ppm hydrogen sulfide for 4 hours. Necrosis and exfoliation of the respiratory and olfactory mucosal cells were observed 1 hour postexposure at concentrations >200 ppm; by 20 hours postexposure, the respiratory epithelium was covered by a layer of deeply basophilic cells containing mitotic figures and severe inflammatory response was noted. The necrosis ultimately ulcerated the respiratory epithelium, causing exposure of the basement membrane (Lopez et al. 1988b). Although some histological changes were observed at 10 and 200 ppm hydrogen sulfide, no dose

response was evident; it appears that a concentration >200 ppm is necessary to induce these lesions (Lopez et al. 1988b).

Similarly, Brenneman et al. (2002) observed bilateral symmetrical mucosal necrosis in the nasal olfactory epithelium and respiratory epithelial regeneration in rats exposed to 200 or 400 ppm hydrogen sulfide for 3 hours; the NOAEL for these effects is 80 ppm. However, the respiratory epithelial was not adversely affected in rats similarly exposed 3 hours/day for 5 days (Brenneman et al. 2002). In these rats, necrotic olfactory epithelium and hyperplastic basal cells were observed in rats exposed to 80, 200, or 400 ppm, but not at 30 ppm. A partial regeneration of the olfactory epithelium was observed 2 weeks after exposure termination and a complete regeneration was observed 6 weeks post-exposure.

Cytochrome *c* oxidase activity in lung mitochondria of F-344 rats was significantly decreased at 50 ppm (15%), 200 ppm (43%), and 400 ppm (68%) hydrogen sulfide compared to controls after a 4-hour exposure (Khan et al. 1990). Cytochrome *c* oxidase activity had returned to normal for animals exposed to 200 ppm, but not for those exposed to 400 ppm, by 24 hours postexposure. Succinate oxidase activity was reduced at 200 ppm (40%) and 400 ppm (63%), but was not affected at 50 ppm (Khan et al. 1990). A 5-week exposure to 10 or 100 ppm hydrogen sulfide (8 hours/day, 5 days/week) also resulted in significant decreases in cytochrome oxidase activity in lung mitochondria (Khan et al. 1998); exposure to 1 ppm did not result in significant alterations.

Significant decreases in numbers of viable pulmonary alveolar macrophages were noted in the lung lavage fluid of male rats exposed for 4 hours to 400 ppm hydrogen sulfide (Khan et al. 1991). This study also showed complete abolition of zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages in animals exposed to 200 or 400 ppm. No changes were noted after exposure to 50 ppm hydrogen sulfide.

Histological changes were characterized in the lungs of male F-344 rats exposed to 83 or 439 ppm for 4 hours (Lopez et al. 1988a). At the low dose, mild perivascular edema was found, but at the high dose, numerous changes were observed, including severe but transient pulmonary edema and fibrocellular alveolitis in proximal alveoli; cytoplasmic blebs in the alveolar endothelium; increased numbers of mitotic figures in the bronchiolar epithelium; minor changes in the alveolar epithelium; and necrosis of the ciliated bronchiolar cells. Moderate-to-massive pulmonary edema was evident in male F-344 rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990), and slight pulmonary congestion was found in male Wistar rats exposed to 75 ppm hydrogen sulfide for 1 hour (Kohno et al. 1991).

The effects of intermediate-duration exposures to hydrogen sulfide have been examined in rats, mice, and pigs. Respiratory effects were not observed in F-344 (CIIT 1983b) or Sprague-Dawley (CIIT 1983c) rats exposed to hydrogen sulfide at concentrations up to 80 ppm 6 hours/day, 5 days/week, for 90 days. However, a re-examination of the histologic specimens from this study (Dorman et al. 2004) found significant increases in the incidence of olfactory neuron loss in Sprague-Dawley and F-344 rats exposed to 30 or 80 ppm and in male rats exposed to 80 ppm; the no-effect levels in these strains were 10 and 30 ppm, respectively. In addition, increases in the incidence of bronchiolar epithelial hypertrophy and hyperplasia were observed in the female Sprague-Dawley rats exposed to 30 or 80 ppm hydrogen sulfide and in male Sprague-Dawley and F-344 rats exposed to 80 ppm. These findings are similar to those of Brenneman et al. (2000) who found significant increases in the incidence and severity of nasal lesions in male Sprague-Dawley rats exposed to hydrogen sulfide for 6 hours/day, 7 days/week for 10 weeks. The nasal lesions, which were limited to the olfactory mucosa, consisted of multifocal, bilaterally symmetrical olfactory neuron loss, and basal cell hyperplasia. The olfactory neuron loss and basal cell hyperplasia was found in most animals exposed to 30 or 80 ppm, but was not found in controls or rats exposed to 10 ppm. At 30 ppm, the severity of the olfactory neuron loss and basal cell hyperplasia was graded as mild to moderate. At 80 ppm, the severity of the olfactory neuron loss was moderate to severe and the basal cell hyperplasia was scored as mild.

Inflammation of the nasal mucosa described as minimal to mild rhinitis was observed in $B6C3F_1$ mice exposed to hydrogen sulfide at 80 ppm for 6 hours/day, 5 days/week for 90 days (CIIT 1983a); these lesions were not observed at 30 ppm. A re-examination of the histological specimens from this study confirmed these results (Dorman et al. 2004) and also found significant increases in the incidence of olfactory neuron loss in the nasal olfactory epithelium of male and female mice exposed to 30 or 80 ppm, but not at 10 ppm.

Three crossbred pigs of unspecified sex were continuously exposed to 0 or 8.5 ppm hydrogen sulfide in inhalation chambers for 17 days (Curtis et al. 1975). No significant changes in body weight gain and no histopathological changes in the respiratory tract (including turbinates, trachea, and lungs) were noted. This study is limited by the number of animals used and because only one exposure concentration was used.

Cardiovascular Effects. Cardiovascular effects have been noted after acute exposures to high concentrations of hydrogen sulfide via inhalation (Arnold et al. 1985). Slight blood pressure increases

were noted in several workers exposed to hydrogen sulfide in a pelt room, however, their electrocardiograms (EKGs) were normal (Audeau et al. 1985). In other instances of hydrogen sulfide poisoning that occurred after a short exposure to high concentrations, no changes in blood pressure were noted despite other cardiac irregularities (Ravizza et al. 1982). Hemodynamic instability was noted in one of two men who survived acute exposure to an unknown concentration of hydrogen sulfide and also swallowed large amounts of manure after entering a partially drained liquid manure pit (Osbern and Crapo 1981). Sinus tachycardia has been noted in men who completely recovered after exposure to hydrogen sulfide (Peters 1981; Ravizza et al. 1982). Supraventricular tachycardia and left bundle block were noted in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material; the effects were temporary (Stine et al. 1976). Extreme tachycardia and hypotension were noted in a woman who attempted to clean a well with muriatic acid and was exposed to an unknown concentration of hydrogen sulfide gas; hypertension was noted in a man exposed during this same incident (Thoman 1969).

EKGs taken on two workers about 2.5 hours after an acute exposure to hydrogen sulfide showed cardiac arrhythmias (Krekel 1964). The workers were exposed for <5 minutes after a spill of sodium sulfide that broke down to release hydrogen sulfide. In one individual, a negative P wave, indicating a substitute rhythm, was noted, while in the other individual, a continuous arrhythmia due to atrial flutter was found. EKGs for both men had returned to normal within 24 hours.

No adverse cardiovascular effects were found when healthy male volunteers were exposed to hydrogen sulfide concentrations up to 5 ppm for >16 minutes after graded exercise performed to exhaustion (Bhambhani and Singh 1991). A study that examined the effects of inhalation of 5 ppm hydrogen sulfide on physiological parameters found no changes in heart rate, blood pressure, percent hemoglobin saturation, perceived exertion, or other parameters in healthy male and female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). A subsequent study examining the effects of inhaling 10 ppm hydrogen sulfide during two 30-minute sessions of submaximal exercise found no significant changes in cardiovascular responses under these conditions (Bhambhani et al. 1997).

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. A significant increase in incidence was found for diseases of the circulatory system (SIR=1.05; p=0.001) among Rotorua residents as compared to all other New Zealand residents. Although previous

monitoring information from Rotorua in 1978 showed a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements over 70 μg/m^3 and 10% over 400 μg/m^3 (Bates et al. 1997), the lack of monitoring information concurrent with these data precludes conclusions with regard to a causal relationship between circulatory system disease and hydrogen sulfide exposures. Using hospital discharge records for 1993–1996, Bates et al. (2002) attempted to examine exposure-related trends for cardiovascular disease among residents of Rotorua. Residents were divided into three exposure categories (low, medium, and high) based on surrogate exposure data. A statistically significant ($p<0.001$) trend for exposure-related increases in the incidence of circulatory system disease was observed. When the circulatory system disease category was further divided into minor disease categories, significant ($p<0.01$) exposure-related trends for cerebrovascular disease and diseases of arteries, arterioles, and capillaries were found. However, no significant increases in SIRs were found for the cerebrovascular disease category. For artery, arteriole, and capillary disease category, the SIRs were significantly elevated for the medium (SIR=1.58, 95% confidence level of 1.17–2.08) and high (SIR=1.66, 95% confidence interval of 1.30–2.09) exposure groups. The lack of exposure data, the assumption that hydrogen sulfide exposure only occurred at home, and the lack of control for potential confounding factors such as smoking and socioeconomic status limit the interpretation of these data.

Studies in experimental animals have reported EKG alterations (e.g., cardiac arrhythmia) following acute-duration exposure to 72–75 ppm for 1.5 hours or less (Kohno et al. 1991; Kosmider et al. 1967); however, the lack of statistical analysis precludes interpretation of these studies. Alterations in heart rate have also been reported. A decrease in heart rate (10–27% of controls) was observed in rats exposed to 75 ppm for 60 minutes (Kohno et al. 1991). In contrast, another study found an increase in heart rates in rats exposed to 100–200 ppm for 1 hour (Higuchi and Fukamachi 1977). The differences may be reflective of the different exposure levels. Data on the cardiotoxicity of hydrogen sulfide following longer-term exposure is limited to a study by CIIT (1983a, 1983b, 1983c). This study found no treatment-related histopathological alterations in the cardiovascular system of F-344 or Sprague-Dawley rats or B6C3F$_1$ mice exposed via inhalation to time-weighted-average (TWA) concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Gastrointestinal Effects. Nausea and vomiting have been noted in several cases of human inhalational hydrogen sulfide poisoning (Allyn 1931; Audeau et al. 1985; Deng and Chang 1987; Krekel 1964; Osbern and Crapo 1981; Thoman 1969).

In two evaluations of the acute health effects associated with communities experiencing episodes of high emissions, significant increases in the reporting of nausea as a symptom have been reported (Haahtela et al. 1992; Marttila et al. 1995). In the first study, increased emissions from a pulp mill resulted in increased concentrations of hydrogen sulfide over 2 days. The highest 4-hour concentration of hydrogen sulfide was 135 μg/m^3 (96.4 ppb) and the 24-hour averages for the 2 days were 35 and 43 μg/m^3 (25 and 31 ppb). Following the high exposure, and then after a low exposure period (hydrogen sulfide level of 0.1 to 3.5 μg/m^3 [0.07–2.5 ppb] for 4 hours), community responses were evaluated with a questionnaire. In this comparison, the concentration of sulfur dioxide was the same. In a study, Marttila et al. (1995) compared community responses using six consecutive questionnaires after three predefined levels of exposure. The three exposure levels were expressed as μg/m^3 of TRS as a way to summarize the complex pollution mixture of hydrogen sulfide, methyl mercaptan, and methylsulfides produced by pulp mills using the sulfate pulping method. The three categories of exposure were low (daily mean of TRS <10 μg/m^3), (medium 10–30 μg/m^3), and high exposure (>30 μg/m^3). An increase in reports of nausea was significant only with the highest level of exposure. Interpretation of these results is complicated by the presence of multiple sulfur compounds as well as other air pollutants. Earlier work indicated that hydrogen sulfide represented two-thirds of the TRS (Marttila et al. 1994a). Concurrent measurements of sulfur dioxide, total suspended particles, and nitrogen oxides for the periods covered by each of the questionnaires, indicated that only sulfur dioxide appeared to co-vary with TRS.

No treatment-related histopathological changes were detected in the gastrointestinal tract of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed via inhalation TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gastrointestinal effects were reported in crossbred pigs exposed to 8.5 ppm hydrogen sulfide for 24 hours/day for 17 days (Curtis et al. 1975).

Hematological Effects. The cyanosis that has been reported in a number of cases of accidental exposure to hydrogen sulfide is believed to result from respiratory distress (Arnold et al. 1985; Burnett et al. 1977; Deng and Chang 1987; Peters 1981; Ravizza et al. 1982; Stine et al. 1976; Tvedt et al. 1991a, 1991b).

Complete blood counts were normal in four individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). Percent hemoglobin saturation was unchanged by inhalation of either 5 ppm hydrogen sulfide by volunteers during 30-minutes of submaximal exercise

(Bhambhani et al. 1994), or 10 ppm hydrogen sulfide during two 30-minute sessions of submaximal exercise (Bhambhani et al. 1997).

Workers who were sometimes exposed to airborne concentrations of >20 ppm hydrogen sulfide did not have any changes in hematological parameters (Ahlborg 1951). Pulp industry workers (n=17) exposed to 8-hour TWA concentrations of 0.05–5.2 ppm hydrogen sulfide had no signs of clinical anemia (Tenhunen et al. 1983). Jappinen and Tenhunen (1990) examined blood sulfide concentration and changes in heme metabolism at 2 hours, 1 week, and 1 month post-hydrogen sulfide poisoning in six cases of occupational exposure. Decreased delta-aminolaevulinic acid synthase activities and erythrocyte protoporphyrin concentrations were noted at the 2-hour and 1-week time periods, but not to the level of significance, and there was no change in heme synthase activity.

No treatment-related changes in hematological parameters were noted in F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed by inhalation to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Musculoskeletal Effects. In a series of reports characterizing the responses of healthy volunteers to low level, short-term exposures to hydrogen sulfide, Bhambhani and his colleagues (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a, 1996b, 1997) concluded that exposures to 5 or 10 ppm hydrogen sulfide via oral inhalation resulted in increases in blood lactate concentrations and a decrease in muscle citrate synthase activity indicative of an inhibition of the aerobic capacity of exercising muscle. Men appeared to be more sensitive to this effect, showing a small response at 5 ppm where women did not show an effect until the 10 ppm level (Bhambhani et al. 1996b, 1997).

No treatment-related histopathological changes were detected in the skeletal muscle, bone marrow, or bone of F-344 or Sprague-Dawley rats or $B6C3F_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Hepatic Effects. Increases in unspecified liver enzyme activities were noted in some of 221 persons exposed by inhalation to hydrogen sulfide (Burnett et al. 1977). No baseline for these effects was available and they were not quantified.

No changes in serum protein, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (serum glutamic oxaloacetic transaminase [SGOT]; aspartate aminotransferase), or alkaline phosphatase

activities were noted in Sprague-Dawley rat dams exposed to 20, 50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al. 1990a). Maternal liver cholesterol levels were increased in Sprague-Dawley dams exposed to 75 ppm, but not 50 ppm, for 7 hours/day from gestation day 6 to postpartum day 21 (Hayden et al. 1990b).

No treatment-related histopathological changes were detected in the livers of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No gross or histopathological lesions were found in the livers of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Renal Effects. Blood urea nitrogen and serum electrolyte levels were normal in several individuals overcome by unknown concentrations of hydrogen sulfide gas in a pelt room (Audeau et al. 1985). One of these four patients had protein and blood in the urine initially, which was not detected upon later testing. Albumin and some granular casts were noted in the urine in another patient, but these findings were transient (Audeau et al. 1985).

F-344 and Sprague-Dawley rats as well as B6C3F_1 mice were exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No treatment-related histopathological changes were detected in the kidneys of these animals and urinalysis findings were negative, indicating no renal effects due to hydrogen sulfide exposure. No gross or histopathological lesions were found in the kidneys of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Endocrine Effects. No studies were located regarding endocrine effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were detected in the pituitary, adrenal, thyroid, or parathyroid glands of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Dermal Effects. Six men lost consciousness after acute hydrogen sulfide exposure; one man with probable exposure to 8–16 ppm had peeling facial skin (Tvedt et al. 1991a, 1991b).

No treatment-related histopathological changes were detected in the skin of F-344 or Sprague-Dawley rats or B6C3F$_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Slate-grey skin discoloration and erythema were noted in rabbits exposed to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942).

Ocular Effects. Ocular effects reported after inhalation exposure are believed to have resulted from direct eye contact with hydrogen sulfide gas. Hydrogen sulfide gas is an eye irritant. Keratoconjunctivitis (sometimes with subsequent infection), punctate corneal erosion, blepharospasm, lacrimation, and photophobia have developed in individuals exposed to brief high-level concentrations of hydrogen sulfide gas (Ahlborg 1951; Luck and Kaye 1989). Hemorrhagic keratoconjunctivitis and subconjunctival hemorrhage were reported in cases of near-lethal poisoning to unknown concentrations of hydrogen sulfide (Deng and Chang 1987; Stine et al. 1976). A retrospective study of 250 Canadian workers who submitted workers' compensation claims for hydrogen sulfide exposure found that 18% had developed conjunctivitis, which persisted for several days in some cases (Arnold et al. 1985). Stinging of the eyes has been reported in acute occupational hydrogen sulfide poisoning (Audeau et al. 1985). None of these reports of ocular exposure suggested that permanent eye effects may occur (Ahlborg 1951; Arnold et al. 1985; Audeau et al. 1985; Deng and Chang 1987; Luck and Kaye 1989; Stine et al. 1976). People exposed to hydrogen sulfide, methyl mercaptan, and methyl sulfides while living in a community around a paper mill reported eye irritation 12 times more often than people without exposure (Jaakkola et al. 1990). These effects were observed at mean annual hydrogen sulfide exposures estimated at 6 μg/m^3 (4.3 ppb). However, the ocular symptoms that were reported may have been due to exposure to peak concentrations of hydrogen sulfide (daily peaks as high as 100 μg/m^3; 70 ppb) and not annual mean concentrations, or may have been due to co-exposure to methyl mercaptan and methyl sulfides. Methyl mercaptan is also an eye irritant (NIOSH 2006) and it was also present at an annual mean concentration of 2–5 μg/m^3 with the highest daily average concentration being 50 μg/m^3 (Jaakkola et al. 1990).

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work, it was indicated that the most reliable monitoring information for hydrogen sulfide in the area came from a monitoring exercise in 1978, which found a median

concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3 (Bates et al. 1997). On the basis of hospital discharge data, significant increases in incidence were found for diseases of the nervous system and sense organs (SIR=1.11; p<0.001) among Rotorua residents as compared to the rest of New Zealand. When incidence rates were examined for minor disease groupings within this group of nervous system and sense organ diseases, significantly increased risks were seen for other disorders of the eye and adnexa (SIR=1.12; p<0.001). At the level of individual diseases, statistically significant incidence ratios were found for cataract (SIR=1.26; p<0.001), disorders of the conjunctiva (SIR=2.09; p<0.001), and disorders of the orbit (SIR=1.69; p=0.005). The effect of hydrogen sulfide on the eye is of considerable importance because ocular effects occur at concentrations that provide no other observable systemic effect (NIOSH 1977a).

Ocular irritation has also been noted after animals were exposed to hydrogen sulfide. Epiphora was noted in F-344 rats exposed to 400 ppm, but not 200 ppm, of hydrogen sulfide for 4 hours (Lopez et al. 1988b). Eye irritation was noted in guinea pigs exposed to 20 ppm of hydrogen sulfide 1 hour/day for 20 days (Haider et al. 1980). No ocular lesions were found upon microscopic examination of the eyes of crossbred pigs exposed to 8.5 ppm of hydrogen sulfide 24 hours/day for 17 days (Curtis et al. 1975).

No treatment-related histopathological changes were detected in the eyes of F-344 or Sprague-Dawley rats or B6C3F$_1$ mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c).

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to hydrogen sulfide.

Pregnant Sprague-Dawley rats exposed to 100 or 150 ppm hydrogen sulfide on gestation days 6–20 showed decreased body weight gains that reached significance at the higher dose. Absolute weight gain (i.e., minus the gravid uterine weight) was significantly depressed at both of these doses. Exposure at 50 ppm hydrogen sulfide had no effect on body weight gain or on absolute weight gain (Saillenfait al. 1989). No effects on body weight were noted in Sprague-Dawley rats exposed to 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks (Gagnaire et al. 1986). No treatment-related body weight changes were noted in F-344 rats exposed to TWA airborne concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983b). However, when Sprague-Dawley rats were exposed on the same regimen, females at 80 ppm showed a significant (10%) decrease in body weight at the end of the study compared to controls, which was not evident at 30 ppm (CIIT 1983c). At 80 ppm,

the body weight of males was significantly less (8%) than controls during weeks 1–3, but the final body weight differences were not significant (CIIT 1983c). Similarly, B6C3F_1 mice of both sexes exposed to TWA concentrations of 80 ppm hydrogen sulfide 6 hours/day, 5 days/week, for 90 days showed decreases in body weight of 7–14% compared to controls; these changes were not observed at 30 ppm (CIIT 1983a). No body weight changes were found in crossbred pigs exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975).

Metabolic Effects. Severe metabolic acidosis developed in a worker exposed to hydrogen sulfide generated from a sodium sulfide waste solution dumped onto acid waste material (Stine et al. 1976). Blood lactate concentrations were significantly increased (65%) compared to controls during exercise in men exposed to 5 ppm hydrogen sulfide via oral inhalation for >16 minutes (Bhambhani and Singh 1991), but not at 2 ppm. Additional studies by the same group (Bhambhani et al. 1994, 1996b) exposed both men and women to 5 ppm hydrogen sulfide during 30 minutes of exercise and failed to observe significant increases in lactate concentrations, but did see a decrease in muscle citrate synthase in men, suggesting that aerobic metabolism was being compromised at this level of exposure.

In a subsequent study, Bhambhani et al. (1997) observed significant increases in blood lactate concentrations in male and female volunteers exposed to 10 ppm hydrogen sulfide, although there was not a significant change in the activities of muscle lactate dehydrogenase, citrate synthase, or cytochrome oxidase.

In Sprague-Dawley rat dams exposed to 20, 50, or 75 ppm of hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21, blood glucose levels were increased about 50% at all exposure concentrations (Hayden et al. 1990a).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after inhalation exposure to hydrogen sulfide.

No treatment-related histopathological changes were found in the spleen or lymph nodes of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm of hydrogen sulfide 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). Pulmonary alveolar macrophage function was studied using lavage fluid from F-344 rats exposed for 4 hours to 50, 200, or

400 ppm hydrogen sulfide (Khan et al. 1991). Although the number of pulmonary alveolar macrophage cells was not influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased at 400 ppm. When the pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, it was found that there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm; these rates were significantly different from controls and were approximately equal to basal cell levels (Khan et al. 1991).

The highest NOAEL values and all reliable LOAEL values for immunological effects in rats and mice exposed in acute- and intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.4 Neurological Effects

Acute human exposure to hydrogen sulfide can result in nausea, headaches, delirium, disturbed equilibrium, poor memory, neurobehavioral changes, olfactory paralysis, loss of consciousness, tremors, and convulsions. Fatigue, poor memory, dizziness, and irritability have been observed in workers chronically exposed to hydrogen sulfide (Beauchamp et al. 1984); however, it is not known if these effects are the result of chronic exposure or due to reoccurring acute exposures.

Available information on the neurotoxic effects of acute exposures to high levels of hydrogen sulfide in humans comes primarily from case reports. In most instances, exposure concentrations were either unknown or estimated. In most cases, the exact exposure duration was not known, but estimated durations ranged from several minutes to an hour. The most commonly reported nonlethal effect found in individuals exposed to high concentrations is unconsciousness followed by apparent recovery, colloquially referred to as knockdown (Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Other described neurological effects in the case reports include disturbed equilibrium, nausea, headache, poor memory, insomnia, irritability, delirium, severe vertigo, unusual sweating, neuropsychological symptoms, convulsions, and tremors (Arnold et al. 1985; Krekel 1964). While deaths were often noted, there were cases in which individuals survived and had complete neurological recovery (Deng and Chang 1987; Krekel 1964; Osbern and Crapo 1981; Ravizza et al. 1982). In a study of the possible effects of exposure to low concentrations of hydrogen sulfide, 3/10 asthmatic volunteers complained of headache after being exposed in a sealed chamber to 2 ppm hydrogen sulfide for 30 minutes (Jappinen et al. 1990).

A few case reports have described permanent or persistent neurological effects in humans following acute inhalation exposure to high concentrations of hydrogen sulfide. One patient developed symptoms of frontal headaches, irritability, poor concentration ability and attention span, and deficits of cortical function tests, including verbal abstraction, attention, and short-term retention 1 month after accidental exposure to unspecified concentrations of hydrogen sulfide (Stine et al. 1976). All effects except headaches resolved by 2 months after the accident. A 5–10-year follow-up re-examination of several individuals who became unconscious after exposure to unspecified concentrations of hydrogen sulfide revealed permanent neurological symptoms (Tvedt et al. 1991a, 1991b) including vision and memory impairment; rigid movements; reduced motor function; slight tremor; ataxia; psychosis; abnormal learning, retention, and motor function; and slight cerebral atrophy. The probable exposure concentration in one of the patients may have exceeded 200 ppm (as measured 2.5 hours after exposure). Divergent reports of the risk of permanent neurological damage due to hydrogen sulfide may result from lack of follow-up after hospital discharge (Tvedt et al. 1991b). Permanent neurologic damage including effects on balance, vibration sense, and impaired verbal and visual recall were observed in one man exposed to a very high concentration (14,000 ppm) of hydrogen sulfide (Kilburn 1993). In another case report, a worker who suffered ‘knockdown’ and presented in a coma, remained in a coma through standard treatment (i.e., sodium nitrite), underwent several treatments with hyperbaric oxygen, and became responsive to simple commands by day 5. However, at the time of discharge, an extensive head injury assessment found effects on speech, attention span, insight, and ability to communicate, as well as a marked impact on visual memory and the ability to acquire, retain, and recall new information. These effects had not resolved by 12 and 18 months after exposure (Snyder et al. 1995). In a somewhat similar scenario, Schneider et al. (1998) describe a case in which another worker lost consciousness when he descended into a 27-foot pit that was part of a sewer construction project. He was overcome by hydrogen sulfide fumes (concentration not specified), fell from a ladder from an unspecified height, and was subsequently removed in a coma and transported to a local trauma center. At the emergency room (and potentially at the site), the patient experienced seizure activity. A body computed tomography (CT) scan showed pulmonary edema while a head CT scan was normal. The patient was transferred to a hyperbaric medicine unit and started on hyperbaric oxygen treatments (starting approximately 10 hours post-episode). Five days later, he recovered consciousness, and by 7 days, his status had improved enough to discontinue hyperbaric oxygen treatments. He was able to feed himself and move with assistance, but had impaired language, memory, and attention, and appeared agitated and restless. Over the course of the next 4 years, the patient was evaluated on a variety of occasions. He continued to show a constellation of deficits, which even 4 years later, included problems with general cognition, motor function, and

cognitive function; some of these symptoms appeared to be alleviated through a combined treatment with fairly high doses of Ritalin and Cyclert drugs, which enhance dopaminergic functioning.

In a case control study of 16 subjects who had been exposed for minutes, hours, or years to hydrogen sulfide, Kilburn (1997) found evidence of permanent neurobehavior impairment in exposed individuals when compared to 353 controls matched for sex, age, and years of education. A large battery of tests was used to evaluate these individuals, including a detailed self-administered questionnaire, complete physical and clinical screen neurologic examinations, as well as a series of neurophysiologic and neuropsychologic tests. Among those who had chronic low-dose exposure, the most sensitive tests were those evaluating balance, simple reaction time, left visual field, and verbal recall. The group exposed to hydrogen sulfide for hours showed additional defects, including impacts on a variety of neuropsychological tests, although remote memory remained intact. The group that experienced momentary knock-down exposure had an even larger suite of deficit cognitive functions, leading the study author to conclude that "...brief high doses were devastating, whereas protracted low doses showed effects on the more sensitive tests."

A 20-month-old child was exposed for nearly 1 year to >0.6 ppm hydrogen sulfide and other emitted chemicals from a coal mine (Gaitonde et al. 1987). Symptoms included ataxia, choreoathetosis, dystonia, and inability to stand. A CT scan of the brain showed bilateral areas of low density in the region of both basal ganglia and surrounding white matter. Neurophysiological investigations of electroencephalography, visual evoked responses, brain stem evoked responses, and peripheral nerve conduction studies were normal. The child's condition improved spontaneously, shortly after hospital admission; after 10 weeks, ataxia had resolved and the choreoathetoid movements were reduced. A repeat brain scan showed complete resolution of abnormalities. The relationship of these complaints to low-level hydrogen sulfide exposure is unclear.

Neurological effects resulting from chronic-duration exposure to hydrogen sulfide in the shale industry have been reported (Ahlborg 1951). Symptoms observed in workers exposed to daily concentrations of hydrogen sulfide that often exceeded 20 ppm included fatigue, loss of appetite, headache, irritability, poor memory, and dizziness. The frequency of fatigue increased with length of employment and the degree of hydrogen sulfide exposure.

In the South Karelia air pollution study, discussed in more detail under respiratory effects, all of the reports found increases in the incidence of headaches or migraines in polluted communities when compared to nonpolluted communities (Jaakkola et al. 1990; Marttila et al. 1994b, 1995; Partti-Pellinen et

al. 1996); however, only in the most recent study did this finding achieve statistical significance. Using a cross-sectional, self-administered questionnaire, this report (Partti-Pellinen et al. 1996) evaluated the increased risk of headache or migraine in adults in a slightly polluted and a reference community. In the polluted community, the mean annual TRS concentrations were 2–3 μg/m^3, the 24-hour concentrations varied between 0 and 56 μg/m^3, and the maximum 1-hour concentration was 155 μg/m^3; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 μg/m^3, the 24-hour concentrations varied between 0 and 24 μg/m^3 and the maximum 1-hour concentration was 152 μg/m^3. In the reference community, the mean sulfur dioxide level was 1 μg/m^3 and the maximum 1-hour concentration was 30 μg/m^3. The residents of the polluted community showed a significantly increased risk of headache both during the previous 4-week period (OR=1.83; 95% CI=1.06–3.15) and the preceding 12 months (OR=1.70; 95% CI=1.01–2.64), when compared to the residents of the reference community, even after adjusting for differences in age, gender, smoking, history of allergic diseases, education, and marital status between the two communities.

In a retrospective epidemiologic study using hospital discharge data from 1981 to 1990, Bates et al. (1998) evaluated the risk of disease to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. Although no information on hydrogen sulfide levels was presented in this report, the authors' previous work indicated that a monitoring exercise in Rotorua in 1978 found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements >70 μg/m^3 and 10% >400 μg/m^3; additionally, elevated concentrations of mercury had previously been found in the hair of residents (Bates et al. 1997). Significant increases in incidence were found for diseases of the nervous system and sense organs (SIR=1.11; $p<0.001$) among Rotorua residents as compared to the rest of New Zealand residents. When the data were stratified by gender and ethnicity, the increased risks remained significant for all but non-Maori men. When incidence rates were examined for minor disease groupings within nervous system diseases, significantly increased risks were seen for other disorders of the central nervous system (SIR=1.22; $p<0.001$) and disorders of the peripheral nervous system (SIR=1.35; $p<0.001$). At the level of individual diseases, statistically significant incidence ratios were found for infant cerebral palsy (SIR=1.42; $p=0.02$), migraine (SIR=1.40; $p=0.002$), other conditions of the brain (SIR=2.50; $p<0.001$), mononeuritis of the upper limbs and mononeuritis multiplex (SIR=1.47; $p<0.001$), and mononeuritis of the lower limbs (SIR=2.06; $p<0.001$). A follow-up study of this population found a significant exposure-related trend ($p<0.001$) for increasing incidence of diseases of the nervous system and sense organs (Bates et al. 2002). In this study, the hospital discharge records were used to obtain disease incidence data; additionally, the affected individuals were divided into three exposure groups (low, medium, and

high) based on their current residence. Actual exposure levels were not monitored; a surrogate for exposure was used. When the nervous system disease incidence was further divided into subcategories, significant trends ($p<0.001$) were found for other disorders of the central nervous system, disorders of the eye and adnexa, and disorders of the ear and mastoid process. The SIRs (95% confidence interval) were significantly elevated in all groups for disorders of the eye and adnexa: 1.47 (1.33–1.63), 1.57 (1.30–1.89), and 2.27 (1.97–2.61) for the low, medium, and high exposure groups, respectively. In the high exposure group, the SIRs were also elevated for other disorders of the central nervous system (2.59, 1.91–3.44), disorders of the peripheral nervous system (2.27, 1.97–2.61), and disorders of the ear and mastoid process (2.00, 1.65–2.40). The lack of exposure data, the assumption that hydrogen sulfide exposure only occurred at home, the assumption that current exposure also represented historical exposure, and the lack of control for confounding variables such as smoking and socioeconomic status limit the interpretation of these data.

ATSDR (Inserra et al. 2004) examined residents of Dakota City, Nebraska for neurobehavioral effects resulting from chronic exposure to ≥90 ppb hydrogen sulfide. Although the 90 ppb level was used as a cut off value, historical monitoring data records showed much higher levels; for example, the outdoor hydrogen sulfide level exceeded 1,000 ppb 275 times in the 1995–1999 time period. Hydrogen sulfide exposure did not appear to adversely affect performance on most neurobehavioral tests; in fact, the hydrogen sulfide exposed groups scored better than the referent group on 21 of the 28 tests, although the differences were not statistically significant. The hydrogen sulfide group did score lower on a memory test (match to sample score) and a test of grip strength, but the differences were not statistically significant.

Rabbits exposed to 72 ppm of hydrogen sulfide for 1.5 hours lost consciousness (Kosmider et al. 1967). Haider et al. (1980) observed behaviors in guinea pigs exposed daily to 20 ppm of hydrogen sulfide for 11 days that were indicative of fatigue, somnolence, and dizziness; no additional information of overt behaviors were provided. Neurochemical analyses revealed decreased cerebral hemisphere and brain stem total lipids and phospholipids. Rats exposed to 800 ppm of hydrogen sulfide for 20 minutes lost consciousness (Beck et al. 1979). Lethargy was observed in rats following exposure to 400 ppm of hydrogen sulfide for 4 hours (Lopez et al. 1988b).

Male Wistar rats were exposed to average concentrations of 100–200, 200–300, 300–400, or 400–500 ppm hydrogen sulfide; at 200–300 ppm, a decreased response rate in a discriminated avoidance task was observed (Higuchi and Fukamachi 1977). Except at the highest concentrations tested, the response

rates and percent avoidances recovered rapidly when ventilation with clean air was provided, although even at 400–500 ppm, they were almost normal the following day (Higuchi and Fukamachi 1977). When these same animals were tested for Sidman-type conditioned avoidance response at response-shock intervals of 10 or 30 seconds, an inverse relationship between hydrogen sulfide concentration and response rate was noted (Higuchi and Fukamachi 1977); this effect dissipated when exposure stopped.

Female NMRI mice were exposed to 100 ppm of hydrogen sulfide for 2 hours at 4-day intervals; excitement was observed (Savolainen et al. 1980). Exposure also resulted in decreased cerebral ribonucleic acid (RNA), decreased orotic acid incorporation into the RNA fraction, and inhibition of cytochrome oxidase. An increase in the glial enzyme marker, 2',3'-cyclic nucleotide-3'-phospho-hydrolase, was seen. Neurochemical effects have been reported in other studies. Decreased leucine uptake and acid proteinase activity in the brain were observed in mice exposed to 100 ppm hydrogen sulfide for 2 hours (Elovaara et al. 1978). Inhibition of brain cytochrome oxidase and a decrease in orotic acid uptake were observed in mice exposed to 100 ppm hydrogen sulfide for up to 4 days (Savolainen et al. 1980).

Significant decreases in motor activity (ambulations and total movements) were observed in rats receiving nose-only exposure to 80, 200, or 400 ppm hydrogen sulfide 3 hours/day for 5 days (Struve et al. 2001). However, a decrease in motor activity was not observed in rats receiving whole-body exposures to 80 ppm 3 hours/day for 5 days (Struve et al. 2001). The study authors did not discuss these conflicting results. In addition, significant impairment of learning and memory, as assessed in a water maze test, was observed in rats receiving nose-only exposure to 400 ppm. However, these results should be interpreted cautiously because the impaired learning and memory may have been secondary to the decrease in motor activity and decreased body temperature also observed in these animals.

A series of intermediate-duration studies conducted by Partlo et al. (2001) used the radial arm maze to assess the effect of hydrogen sulfide on learning and memory in rats exposed to 125 ppm hydrogen sulfide 4 hours/day, 5 days/week for 5–11 weeks. In the first study, the rats were trained on the radial arm maze prior to hydrogen sulfide exposure; 5 weeks of hydrogen sulfide exposure did not adversely affect post-exposure performance on the maze, suggesting that 5 weeks of exposure to hydrogen sulfide did not adversely affect memory. In the second study, the rats were exposed to hydrogen sulfide and trained on the maze daily for 11 weeks. The results of this study suggest that hydrogen sulfide did not interfere with acquisition of the maze task, but did adversely affect performance rate. In the third study, the rats from the second study were retrained on a modified radial arm maze without additional exposure

to hydrogen sulfide. These results suggested that the hydrogen sulfide-exposed rats had difficulty re-learning a complex task.

The intermediate-duration effects of hydrogen sulfide on neurological function were examined by the measurement of motor and sensory nerve conduction velocities of the tail nerve or morphology of the sciatic nerve (Gagnaire et al. 1986). Male Sprague-Dawley rats were exposed to 0 or 50 ppm hydrogen sulfide for 5 days/week, for 25 weeks. The study authors did not report the duration of exposure to hydrogen sulfide per day. No neurotoxic effects were observed in the rats.

Neurologic function and neuropathology were evaluated in Sprague-Dawley rats exposed to 0, 10, 30, or 80.0 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983c). Neurological function evaluation included: an assessment of posture; gait; tone of facial muscles; pupillary, palpebral, extensor thrust; and crossed-extensor thrust reflexes. Besides routine neuropathologic examinations, special studies included an examination of teased fibers from muscular and sural branches of the tibial nerve together with specimens from cervical and lumbar spinal cord. Absolute brain weights were decreased (5%) in male rats exposed to 80 ppm hydrogen sulfide in this study; however, there were no treatment-related effects on neurological function or neuropathology. No signs of neurotoxicity were noted in a similar study in which F-344 rats were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide for 90 days (CIIT 1983b). Likewise, no treatment-related neurological effects were observed in male and female $B6C3F_1$ mice exposed to 0, 10.1, 30.5, or 80.0 ppm hydrogen sulfide for 90 days (CIIT 1983a).

The highest NOAEL values and all reliable LOAEL values for neurological effects in rats, guinea pigs, mice, and rabbits from acute- or intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

There are limited data on the reproductive toxicity of hydrogen sulfide in humans. Hemminki and Niemi (1982) examined the spontaneous abortion rate in relationship to maternal and paternal occupation and residential environmental pollution in an industrial community in Finland. Women who were employed in rayon textile and paper products jobs had an increased rate of spontaneous abortions ($p<0.10$), as did women whose husbands worked in rayon textile or chemical processing jobs. This study also examined the possible relationship between exposure to sulfur dioxide, hydrogen sulfide, and carbon disulfide and the occurrence of spontaneous abortions. A non-statistically significant increase in the incidence of

spontaneous abortion was observed in women living in areas with hydrogen sulfide concentrations exceeding 2.85 ppm. Interpretation of these results are limited by the lack of control of other potential confounding variables, particularly occupational exposure to other chemicals. In a retrospective study of spontaneous abortions in a large population of women working in the petrochemical industry in China, Xu et al. (1998) reported a significantly increased risk of spontaneous abortion with frequent exposure to petrochemicals (OR of 2.7; 95% CI=1.8–3.9). When the risk associated with exposure to specific chemicals was examined, exposure to hydrogen sulfide was found to have an OR of 2.3 (95% CI=1.2–4.4).

No treatment-related histopathological changes were found in male or female reproductive organs of F-344 or Sprague-Dawley rats or B6C3F_1 mice exposed to TWA concentrations of 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days (CIIT 1983a, 1983b, 1983c). No significant alterations in gestation length, viability, or litter size were observed in Sprague-Dawley rats exposed to 0, 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day on gestation days 6–21 (Hayden et al. 1990b). An apparent increase in parturition time was observed in the hydrogen sulfide-exposed dams; the mean lengths of parturition were 105.0, 148.8, and 117.5 minutes, compared to 85.2, 124, and 82.5 minutes in the three control groups; these data were not statistically analyzed. The study authors noted that increased parturition time was observed in 6 out of 18 exposed animals and in 1 of 17 controls. Dorman et al. (2000) did not find any significant alterations in gestation length in Sprague-Dawley rats exposed to 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 7 days/week for 2 weeks prior to mating with exposed males, during the 2 week mating period, and on gestational days 0–19. This study also found no significant alterations in fertility (as assessed by mating index, fertility index, postimplantation loss, late resorptions, or still births), number of females with live pups, litter size, or number of implants per female. No histological alterations in the reproductive organs and accessory sex organs of rats in the controls and 80 ppm group were found; a slight, nonstatistically significant increase in the incidence of testicular degeneration was observed at 80 ppm. Additionally, no significant alterations in sperm count or morphology were observed.

The highest NOAEL values for reproductive effects in rats and mice from intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to hydrogen sulfide.

No changes in serum protein, LDH, SGOT, or alkaline phosphatase activities were noted in the offspring of Sprague-Dawley rats exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 1 through postnatal day 21 (Hayden et al. 1990a). No effects on blood glucose were noted in the offspring, although glucose levels were increased by about 50% in dams at all exposure concentrations on postnatal day 21 (Hayden et al. 1990a). In a second study, these authors (Hayden et al. 1990b) found a dose-related increase in parturition time in animals exposed to 20, 50, or 75 ppm hydrogen sulfide for 7 hours/day from gestation day 6 until postpartum day 21. The study also showed developmental delays in pinna attachment and hair growth, but these effects were not dose related.

No fetal effects were noted in a dose range-finding developmental study in which pregnant Sprague-Dawley rats were exposed to 150 ppm hydrogen sulfide on gestation days 6–20, despite body weight loss in the dams (Saillenfait et al. 1989).

No significant alterations in the incidence of structural anomalies were found in the offspring of Sprague-Dawley rats exposed to 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 7 days/week on gestational days 0–19 (Dorman et al. 2000). Continued exposure on postnatal days 5–18 did not result in developmental delays (pinnae detachment, surface righting, incisor eruption, negative geotaxis, and eyelid detachment), performance on developmental neurobehavioral tests (motor activity, passive avoidance, acoustic startle, or functional observation battery), or brain histopathology.

An examination of Purkinje cells from Sprague-Dawley rat pups exposed to 20 or 50 ppm hydrogen sulfide for 7 hours/day from gestation day 5 through postpartum day 21 showed severe alterations in the architecture and growth characteristic of the Purkinje cell dendritic fields compared to controls (Hannah and Roth 1991). The study did not mention whether any maternal effects were observed; however, the authors did indicate that “these findings suggest that developing neurons exposed to low concentrations of hydrogen sulfide are at risk of severe deficits.” Two studies by Hannah et al. (1989, 1990) examined the effects of prenatal exposure to hydrogen sulfide on amino acid levels in the brain. In the first study, pregnant Sprague-Dawley rats were exposed to 75 ppm hydrogen sulfide for 7 hours/day, from postcoitus day 5 to postpartum day 21 (Hannah et al. 1989). Aspartate, glutamate, and GABA in the cerebrum and

cerebellum were significantly reduced (about 20%) compared to controls by postpartum day 21. Taurine levels of the offspring were initially 25% higher than controls but had returned to control range by postpartum day 21; taurine levels were not measured in dams. In the 1990 study, pregnant Sprague-Dawley rats were exposed to 50 ppm hydrogen sulfide for 7 hours/day, from postcoital day 6 to postpartum day 21 (Hannah et al. 1990). In this study, maternal taurine levels were determined on parturition and on postpartum day 21. Taurine in maternal plasma was 30% higher than controls; taurine levels were not determined in offspring, so relating these levels to high taurine levels found in offspring in the 1989 study is speculative.

Further investigation into the developmental neurological effects of hydrogen sulfide was undertaken by Skrajny et al. (1992). Pregnant Sprague-Dawley rats were exposed to 20 or 75 ppm hydrogen sulfide 7 hours/day from gestation day 5 to postpartum day 21; separate control groups were used for each exposure level. Exposure to 20 ppm caused significant increases compared to controls in serotonin levels in the frontal cortex on postpartum day 21. Exposure to 75 ppm hydrogen sulfide caused significant increases compared to controls in levels of serotonin in the cerebellum and cortex on postpartum days 14 and 21. Norepinephrine levels were significantly increased compared to controls at 75 ppm in the cerebellum and the frontal cortex. At 20 ppm, norepinephrine levels were below control levels by days 14 and 21, and in the cerebellum, levels fluctuated but were normal by postpartum day 21 (Skrajny et al. 1992). In a subsequent study using the same exposure regimen (i.e., between day 5 postcoital until day 21 postnatal), but following the monoamine levels in various regions of the brain up to 60 days postnatal, Roth et al. 1995 found that the alterations of monoamine levels observed at day 21 postnatal (the last day of exposure) gradually returned to control values by day 45.

The highest NOAEL and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.1.7 Cancer

There was no increase in cancer incidence noted in a residential cohort study of individuals living downwind from natural gas refineries in Alberta, Canada, from 1970 to 1984 (Schechter et al. 1989). In a retrospective epidemiologic study using cancer registry data from 1981 to 1990, Bates et al. (1998) evaluated the risk of cancer to known target organ systems of hydrogen sulfide toxicity in residents of Rotorua, a New Zealand city that uses geothermal energy for industrial and domestic heating purposes. No information on hydrogen sulfide levels was presented in this report, but the authors indicate concerns

that exposures to hydrogen sulfide and/or mercury from geothermal sources could have health impacts. In their previous work, it was indicated that the most reliable monitoring information for hydrogen sulfide in the area came from a monitoring exercise in 1978 that found a median concentration of hydrogen sulfide of 20 μg/m^3, with 35% of the measurements over 70 μg/m^3 and 10% over 400 μg/m^3 (Bates et al. 1997). Based on the cancer registry information, these workers found a significantly increased risk of nasal cancers (SIR=3.17; p=0.01) among Rotorua residents as compared to the rest of the population of New Zealand. However, since this is a rare cancer, this finding is based on only four cancers. Because the population of Rotorua has a higher percentage of Maoris than the rest of New Zealand, these researchers also examined their data stratified by ethnicity and sex and found a significantly increased risk of cancers of the trachea, bronchus, and lung (SIR=1.48; p=0.02) among female Maoris in Rotorua as compared to female Maoris in the rest of New Zealand. Differences in smoking history between these two populations were not sufficient to explain the observed differences in risk. The authors concluded that the lack of adequate exposure information did not permit findings of causal relationships between hydrogen sulfide and cancer incidence. The potential co-exposure to mercury also confounds the interpretation of these results.

No studies were located regarding cancer effects in animals after inhalation exposure to hydrogen sulfide.

3.2.2 Oral Exposure

3.2.2.1 Death

No studies were located regarding death in humans or animals after oral exposure to hydrogen sulfide.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or metabolic effects after oral exposure to hydrogen sulfide.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to hydrogen sulfide.

Diarrheic digestive disorder was observed in adult pigs fed hydrogen sulfide at a dose level of 15 mg/kg/day for a few days (Wetterau et al. 1964). The study authors reported that in a repeat study using younger pigs that weighed less, no diarrheic disorder was noted.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to hydrogen sulfide.

Decreased body weight gain (48.2 kg total weight gain in treated animals versus 62.5 kg total weight gain in controls) was observed in pigs fed hydrogen sulfide at a dose level of 6.7 mg/kg/day for 105 days (Wetterau et al. 1964).

No studies were located regarding the following health effects in humans or animals after oral exposure to hydrogen sulfide:

3.2.2.3 Immunological and Lymphoreticular Effects

3.2.2.4 Neurological Effects

3.2.2.5 Reproductive Effects

3.2.2.6 Developmental Effects

3.2.2.7 Cancer

3.2.3 Dermal Exposure

3.2.3.1 Death

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

A study by Laug and Draize (1942) reported death in two out of three rabbits exposed to unknown concentrations of hydrogen sulfide through either clipped, intact, or abraded skin. One rabbit with intact skin exposed to hydrogen sulfide for 2 hours survived, while another died in this interval. The rabbit exposed to hydrogen sulfide through abraded skin also died (Laug and Draize 1942). When two guinea pigs were exposed to unknown concentrations of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen, neither died (Walton and Witherspoon 1925). However, both guinea pigs that had their entire shaved torso (about 50% body area) exposed to an unknown concentration of hydrogen sulfide

died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were seen in a dog with shaved abdomen exposed full body (except head) to unknown concentrations of hydrogen sulfide in a chamber for 1 hour (Walton and Witherspoon 1925).

3.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans or animals after dermal exposure to hydrogen sulfide. However, several sources indicate that care must be taken with liquefied hydrogen sulfide in order to avoid frostbite (Agency for Toxic Substances and Disease Registry 1994; NIOSH 2006).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after dermal exposure to hydrogen sulfide.

3.2.3.4 Neurological Effects

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

No clinical signs of neurotoxicity were seen in two guinea pigs exposed to an unknown concentration of hydrogen sulfide gas for 60 minutes on a small area of their shaved abdomen (Walton and Witherspoon 1925). A dog exposed to an unknown concentration of hydrogen sulfide for 1 hour showed no clinical signs of neurotoxicity (Walton and Witherspoon 1925).

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

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

No studies were located regarding genotoxicity in humans after inhalation exposure to hydrogen sulfide.

No mutagenicity was observed with hydrogen sulfide gas in Ames assays using *Salmonella typhimurium* TA97, TA98, and TA100 strains, either with or without S9 liver fractions, of male Syrian golden hamsters or Sprague-Dawley rats that had been induced with 500 mg/kg Aroclor 1254 (EPA 1984). However, it should be noted that the concentration of hydrogen sulfide gas was limited by its solubility in ethanol, which was the test solvent (EPA 1984). The highest dose that could be obtained was 1,750 µg/plate.

3.4 TOXICOKINETICS

Although hydrogen sulfide is primarily absorbed through the lungs, it can also be absorbed through the gastrointestinal tract and intact skin (Laug and Draize 1942; Wetterau et al. 1964). It is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification of hydrogen sulfide is oxidation in the liver, the methylation pathway also serves as a detoxification route (EPA 1987a; Weisiger and Jakoby 1979). The major oxidation product of sulfide is thiosulfate, which is then believed to be converted to sulfate and subsequently excreted in urine (Bartholomew et al. 1980). Hydrogen sulfide is widely distributed in the body. Sulfides have been found in the liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure. Hydrogen sulfide is excreted primarily as sulfate (free sulfate or thiosulfate) in the urine. It is also excreted unchanged in exhaled air and in feces and flatus.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Hydrogen sulfide is absorbed rapidly through the lungs (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Deng and Chang 1987; Hagley and South 1983; Kimura et al. 1994; NIOSH 1989; Osbern and Crapo 1981; Parra et al. 1991). Inhalation absorption of lethal concentrations of hydrogen sulfide is rapid in humans, and effects can occur within seconds to minutes. Inhalation is the most common route of hydrogen sulfide exposure. Hydrogen sulfide dissociates at physiological pH to the hydrogen sulfide anion, which is probably the absorbed form (WHO 1987). No quantitative data are available regarding the absorption of hydrogen sulfide in humans.

Animal data, while demonstrating that absorption of hydrogen sulfide via the lungs occurs readily and rapidly, are not sufficient to quantitatively determine the proportion of an inhaled dose that is absorbed (Beck et al. 1979; Kage et al. 1992; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al. 1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981). No physiologically based pharmacokinetic (PBPK) models have been developed to provide estimates of hydrogen sulfide absorption.

3.4.1.2 Oral Exposure

Hydrogen sulfide exists as a gas; therefore, oral exposure to hydrogen sulfide will not normally occur. No studies were located regarding absorption in humans after oral exposure to hydrogen sulfide. Some case reports showing accidental oral ingestion of liquid manure or other substances that might contain hydrogen sulfide exist, but in all of these cases, the ingestion was secondary to being "knocked down" by inhalation of hydrogen sulfide (Freireich 1946; Imamura et al. 1996; Kimura et al. 1994; Osbern and Crapo 1981).

One animal study suggests that hydrogen sulfide can be absorbed through the gastrointestinal tract. A study where pigs were fed diets containing dried greens with levels of hydrogen sulfide of 1.5, 3.1, or 6.7 mg/kg/day for 105 days indicated that hydrogen sulfide is absorbed following ingestion (Wetterau et al. 1964).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption in humans after dermal hydrogen sulfide exposure.

Animal data have shown that dermal hydrogen sulfide absorption can occur, although large surface areas of skin must be exposed. Trunk fur of rabbits was clipped for exposure to unknown concentrations of hydrogen sulfide gas for 1.5–2 hours; evidence for the absorption of hydrogen sulfide included both the death of the animals and a positive sulfide reaction of expired air with lead acetate paper (Laug and Draize 1942). No evidence of dermal absorption was found in two guinea pigs exposed to unknown concentrations of hydrogen sulfide gas for 1 hour on a small area of their shaved abdomens (Walton and Witherspoon 1925). Dermal absorption was indicated, however, when the entire torso of guinea pigs was exposed to hydrogen sulfide gas and the animals died after about 45 minutes (Walton and Witherspoon 1925). No clinical signs of toxicity were reported in a dog that received full-body exposure (except head) to unknown concentrations of hydrogen sulfide (Walton and Witherspoon 1925).

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Few human data are available regarding tissue distribution after inhalation exposure to hydrogen sulfide. One case study reported sulfide (as bis[pentafluourobenzyl]sulfide) distribution in three of four men who drowned after being overcome, presumably, by hydrogen sulfide and falling unconscious into a lake in Japan (Kimura et al. 1994). Concentrations of hydrogen sulfide gas were estimated to be 550–650 ppm, based upon extrapolation of tissue concentrations from rat studies (Kimura et al. 1994; Nagata et al. 1990). Initial blood sulfide concentrations determined 2–3 hours postmortem in these individuals were 0.1, 0.2, and 0.08 μg/g tissue, while at 24 hours after death, the levels were 0.5 μg/g, 0.23 μg/g, and undetected, respectively. At 24 hours after death, sulfide concentrations in the brains of these individuals were 0.2, 0.4, and 1.06 μg/g, and lung concentrations were 0.68, 0.21, and 0.23 μg/g. Based on a study in rats by this same group of researchers (Nagata et al. 1990) that showed little or no increase in sulfide concentrations in rat lung and brain 24 hours after death, as well as a lack of sulfide in these tissues in control rats, Kimura et al. postulated that the sulfide levels observed in the brain and lungs in the human study may be indicators of tissue levels at the time of death (Kimura et al. 1994). Sulfide was detected in liver (1.30–1.56 μg/g), spleen (0.32–0.64 μg/g), and kidney (0.47–1.50 μg/g) (Kimura et al. 1994). Hydrogen sulfide levels of 0.92 μg/g in blood, 1.06 μg/g in brain, 0.34 μg/g in kidney, and 0.38 μg/g in

liver were detected at autopsy in a man who was overcome by hydrogen sulfide in a tank (Winek et al. 1968). Hydrogen sulfide concentrations in the tank after the accident were 1,900–6,100 ppm (Winek et al. 1968).

Data from animal studies suggest that the distribution of inhaled hydrogen sulfide is rapid and widespread, while storage of hydrogen sulfide in the body is limited by rapid metabolism and excretion. Adult male rats exposed to 550 or 650 ppm hydrogen sulfide until death had tissue samples taken at 0, 4, 24, and 48 hours after death (Nagata et al. 1990). Sulfide concentrations were measured 1, 7, and 30 days later. Immediately after death, sulfide concentrations in whole blood were 0.48 µg/g in exposed animals and were nondetectable in control animals. Sulfide concentrations rapidly increased with time after death in both control and treated animals. Significant increases in sulfide concentrations were found in the lung (0.60 µg/g), brain (0.31 µg/g), thigh muscle (0.21 µg/g), and abdominal muscles (0.22 µg/g), as compared to controls (tissues collected immediately after death) (Nagata et al. 1990). Liver and kidney samples had similar sulfide concentrations in both exposed and control groups when taken immediately after death. Certain tissues (blood, liver, and kidneys) exhibited an increase in sulfide concentration with time after death, whether hydrogen sulfide exposure occurred or not, while other tissues (lung, brain, and muscle) had little or no change in sulfide concentration (Nagata et al. 1990).

Distribution of hydrogen sulfide in male Wistar rats was examined by Kohno et al. (1991). Animals exposed to 75 ppm hydrogen sulfide for 20, 40, or 60 minutes showed essentially the same distribution of hydrogen sulfide irrespective of duration: 10 µg/mL blood, 25 µg/g brain, 20 µg/g lung, 37 µg/g heart, 20 µg/g liver, 25 µg/g spleen, and 30 µg/g kidney. The levels in the brain, lung, heart, liver, spleen, and kidney were significantly ($p>0.01$) higher than blood levels after 20 minutes of exposure.

Japanese white rabbits exposed to 500–1,000 ppm of hydrogen sulfide (the lethal concentration), for 60 minutes, had thiosulfate concentrations of 0.08 µmol/mL in blood, 0.095 µmol/g in lung, and 0.023 µmol/g in brain (Kage et al. 1992). Little or no thiosulfate was found in the liver, kidney, or muscle. When rabbits were exposed to 100–200 ppm of hydrogen sulfide for 60 minutes, blood thiosulfate levels decreased from 0.061 µmol/mL immediately postexposure to a trace level at 2 hours postexposure (Kage et al. 1992).

3.4.2.2 Oral Exposure

No studies were located regarding tissue distribution in humans or animals after oral exposure to hydrogen sulfide.

3.4.2.3 Dermal Exposure

No studies were located regarding tissue distribution in humans or animals after dermal exposure to hydrogen sulfide.

3.4.2.4 Other Routes of Exposure

No studies were located regarding tissue distribution in humans or animals after hydrogen sulfide exposure by other routes.

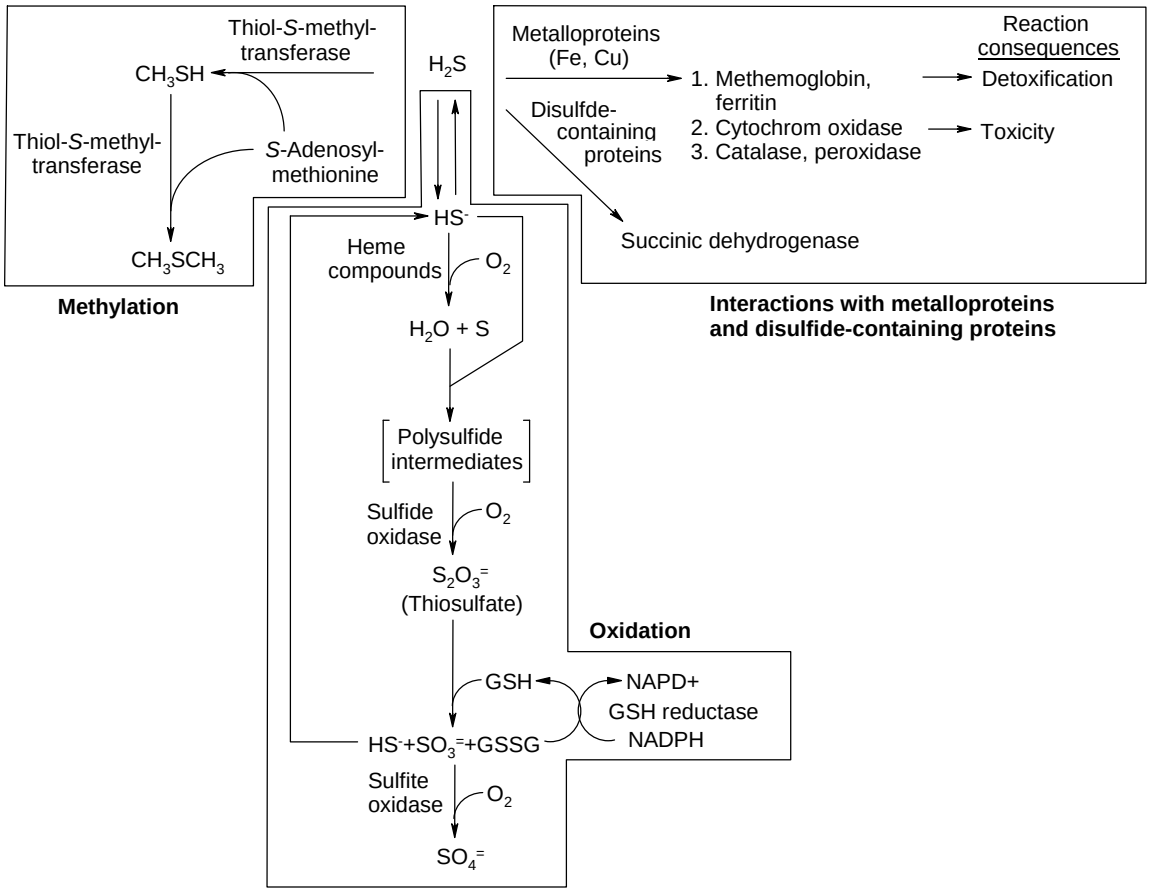
3.4.3 Metabolism

Hydrogen sulfide metabolism occurs through three pathways: oxidation, methylation, and reaction with metallo- or disulfide-containing protein (Beauchamp et al. 1984; EPA 1987a). Hydrogen sulfide is primarily detoxified by oxidation reactions to sulfate (Tabacova 1986). Hydrogen sulfide can also be detoxified by methylation (EPA 1987a; Weisiger and Jakoby 1979). The proposed detoxification pathways most currently accepted for the metabolism of hydrogen sulfide are shown in Figure 3-2 and include oxidation and methylation, as well as the toxic pathways resulting from interactions with metalloproteins and disulfide-containing proteins.

The major metabolic pathway for hydrogen sulfide in the body is the oxidation of sulfide to sulfate, which is excreted in the urine (Beauchamp et al. 1984). The major oxidation product of sulfide is thiosulfate, which is then converted to sulfate; the primary location for these reactions is in the liver (Bartholomew et al. 1980).

Urinary thiosulfate levels were measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30–45 minutes and compared to levels in unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). Very little urinary thiosulfate was excreted in controls (2.9 μmol/mmol creatinine).

Figure 3-2. Metabolic Pathways of Hydrogen Sulfide



Source: Adapted from Beauchamp et al. 1984

The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and decreased to control levels by 17 hours postexposure (Kangas and Savolainen 1987). Most absorbed hydrogen sulfide was already oxidized by 15 hours postexposure (Kangas and Savolainen 1987). This study was limited by the lack of summary data on exposed individuals and inadequate data regarding the numbers of subjects. Using perfused rat liver, Bartholomew et al. (1980) found that there was a rapid oxidation of ^{35}S-sulfide to sulfate. Furthermore, there was a decrease in thiosulfate released from the liver when nonlabelled thiosulfate was added to the perfusion system, suggesting that thiosulfate may act as an intermediate in the oxidation to sulfate (Bartholomew et al. 1980).

Japanese white rabbits exposed to 500–1,000 ppm hydrogen sulfide (the lethal concentration, for 14–30 minutes) had thiosulfate concentrations of 0.08 μM/mL in blood, 0.095 μM/g in lung, and 0.023 μM/g in brain (Kage et al. 1992). Although sulfide was not detected in blood or urine samples of rabbits exposed to a concentration of 100–200 ppm hydrogen sulfide for 60 minutes, thiosulfate levels were highest (1.2 μM/mL) 1–2 hours after exposure and could still be detected in urine 24 hours after exposure (Kage et al. 1992). Thiosulfate levels in blood peaked (0.061 μM/mL) immediately after exposure and were undetectable after 4 hours (Kage et al. 1992).

Evidence for the methylation of hydrogen sulfide comes primarily from *in vitro* studies of Sprague-Dawley rats' intestinal mucosa (Weisiger et al. 1980). Thiol *S*-methyltransferase catalyzed the methylation of hydrogen sulfide to methanethiol (CH_3SH). Methanethiol can act as a substrate for another methylation also catalyzed by thiol *S*-methyltransferase, yielding dimethylsulfide (CH_3SCH_3). The activity of thiol *S*-methyltransferase was widely distributed, with the greatest in cecal and colonic mucosa, liver, lung, and kidney, and was also found in other parts of the intestine and stomach, spleen, heart, and skeletal muscle. No enzyme activity was found in the feces. Although it has been postulated that methylation is a method of detoxification of hydrogen sulfide, a constituent of human flatus produced in the intestine, the extent to which the toxicity of exogenous hydrogen sulfide is attenuated by methylation is not known.

The interaction of hydrogen sulfide with metalloproteins was postulated because the mechanism of toxicity for hydrogen sulfide is the inhibition of cytochrome oxidase and thus, inhibition of the electron transport system. It appears that hydrogen sulfide interacts with other metalloproteins and may represent a detoxification pathway in some instances (Beauchamp et al. 1984). Reduction of disulfide bridges by hydrogen sulfide was suggested by Smith and Abbanat (1966), who found that mice were protected from lethal concentrations of hydrogen sulfide by the administration of oxidized glutathione. This protection

was not afforded by the administration of reduced glutathione. The study authors believed that the disulfide linkage of the oxidized glutathione interacted with the hydrosulfide, which prevented the reaction of sulfide with other sites (Smith and Abbanat 1966). This is attributed to the polarizability of the disulfide bond. The nucleophilic sulfhydryl group of hydrogen sulfide reacts with the δ^+ of the disulfide bond, thus converting it to a less toxic product.

No studies were located regarding metabolism in humans or animals after oral, dermal, or other routes of exposure to hydrogen sulfide.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

The major metabolic pathway for hydrogen sulfide in the body is oxidation of sulfide to sulfate, with the sulfate being excreted in the urine (Beauchamp et al. 1984). Thiosulfate excretion was measured in volunteers exposed to 8, 18, or 30 ppm of hydrogen sulfide for 30–45 minutes and compared to that of unexposed individuals at a pelt processing plant (Kangas and Savolainen 1987). The study did not report the summary results of all exposed individuals; however, data from one individual exposed to 18 ppm hydrogen sulfide for 30 minutes found urinary thiosulfate concentrations of approximately 2, 4, 7, 30, and 5 μM/mM creatinine at 1, 2, 5, 15, and 17 hours postexposure, respectively. The highest urinary thiosulfate levels among exposed individuals occurred 15 hours after exposure and dropped to control levels by 17 hours postexposure.

Kage et al. (1992) evaluated sulfide and thiosulfate levels in the blood and urine of Japanese white rabbits exposed to 100–200 ppm for 60 minutes and concluded that thiosulfate was a better marker for exposure since it could be detected immediately in the blood, but also was detectable in the urine 24 hours after exposure. In the blood, thiosulfate levels decreased from 0.061 μM/mL immediately following exposure to an undetectable amount after 4 hours (Kage et al. 1992). In urine samples from these same animals, thiosulfate levels were highest (1.2 μM/mL) 1–2 hours after exposure, but were still detectable after 24 hours of exposure at slightly higher level than that of control (Kage et al. 1992).

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans or animals after oral exposure to hydrogen sulfide.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to hydrogen sulfide.

Excretion of hydrogen sulfide was documented after dermal exposure in rabbits. Trunk fur of rabbits was clipped and left intact or abraded for exposure to hydrogen sulfide gas (unknown concentrations) for 1.5–2 hours; the animals then breathed clean air (Laug and Draize 1942). Evidence for the excretion of hydrogen sulfide by the rabbits was a sulfide reaction of the expired air with lead acetate paper (Laug and Draize 1942). Sulfides in the expired air were noted in one rabbit with intact skin after 7 minutes of exposure. This study was limited by the lack of measurement of exposure concentrations and the small number of animals used.

3.4.5 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 the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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) are 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 3-3 shows a conceptualized representation of a PBPK model.

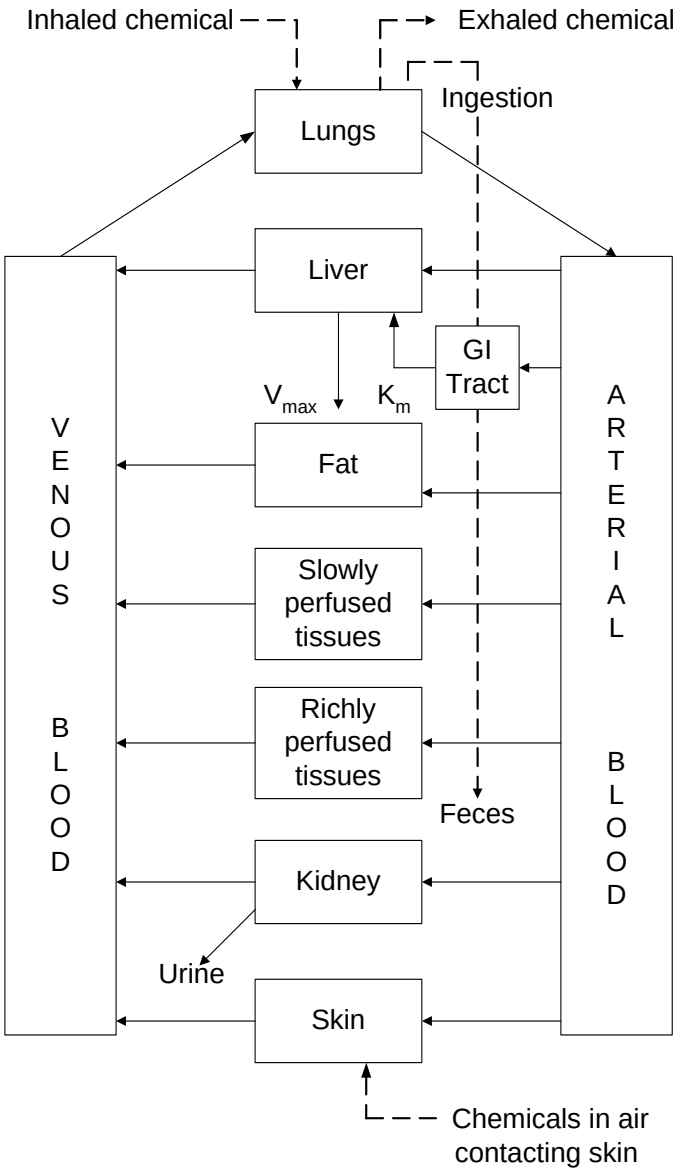
No PBPK models have been developed for hydrogen sulfide.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Hydrogen sulfide is primarily absorbed through the lungs. It can also be absorbed through the gastrointestinal tract and the skin. Hydrogen sulfide is widely distributed in the body after inhalation exposure. Based on analyses of tissues from humans who died after accidental exposure, sulfides have

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



Source: Adapted from Krishnan et al. 1994

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.

been detected in the liver, blood, brain, lungs, spleen, and kidneys. Hydrogen sulfide is metabolized by oxidation, methylation, and reaction with metalloproteins or disulfide-containing proteins. The major metabolic pathway for detoxification of hydrogen sulfide is oxidation of the sulfide to sulfate in the liver. Hydrogen sulfide is excreted primarily as sulfate in the urine.

3.5.2 Mechanisms of Toxicity

Exposure to hydrogen sulfide at concentrations of 500 ppm and greater causes an initial increase in the rate of respiration as a result of the stimulation of the carotid bodies, chemosensors associated with ventilatory control (Ammann 1986). Under normal conditions, these chemosensors stimulate ventilation of the lung during extreme cases in which a significant decrease in the partial pressure of oxygen in the arterial blood traveling to the head occurs (Ammann 1986). This action results in an increase in the number of impulses originating from the chemosensors to the respiratory center in the brain. The rate and depth of ventilation increases to the point of hyperpnea (rapid, deep breathing).

Direct inhibition of cellular enzymes has been postulated as one of many underlying mechanisms of toxicity of hydrogen sulfide (Beauchamp et al. 1984; Deng 1992). In particular, cytochrome oxidase, an enzyme involved in cellular oxidative processes and energy production, has been implicated. Inhibition of cytochrome oxidase is believed to disrupt the electron transport chain and to significantly impair oxidative metabolism, leading to anaerobic metabolism, severely decreased ATP production with curtailed cellular energy generation, and the generation of lactic acid. Nervous and cardiac tissues, which have the highest oxygen demand, are especially sensitive to the disruption of oxidative metabolism (Ammann 1986). In the central nervous system, this effect may result in death from respiratory arrest.

Inhibition of cytochrome oxidase by hydrogen sulfide is similar to that of cyanide (Smith and Gosselin 1979). Although the suggestion has been frequently made that the effects of hydrogen sulfide on nervous tissue are, as with cyanide, simply due to inhibition of oxidative metabolism, recent authors suggest that this is not the case. Reiffenstein et al. (1992) examined this issue and concluded that while treatment with hydrogen sulfide and anoxic conditions arrive at the same end point, there are pharmacological dissimilarities. Baldelli et al. (1993) investigated the mechanism of toxicity associated with hydrogen sulfide exposure (achieved by intravenous injection of sodium sulfide) and concluded that it resulted not from a direct toxicity on central nervous system neurons (i.e., a ‘cerebral necrosis’ due to poisoning of mitochondria respiration), but rather, from an indirect effect associated with a profound hypotension most likely due to cardiotoxicity. These authors emphasized the importance of immediate cardiopulmonary

resuscitation as a way to prevent the delayed toxicity associated with hydrogen sulfide "knock-down" exposures.

An electrophysiological study of the effects of hydrogen sulfide on membrane and synaptic properties of dorsal raphe serotonergic cells in an *in vitro* rat brain-stem slice preparation has elucidated a possible mechanism of neurotoxicity of hydrogen sulfide (Kombian et al. 1993). These neurons are considered to play an important role in central nervous system control of respiratory rhythm. Hydrogen sulfide has been shown to produce two reversible, concentration-dependent effects on the resting membrane properties of the dorsal raphe neurons. Some neurons (14%) responded to hydrogen sulfide with an outward current accompanied by an increase in conductance, while 39% of the neurons responded with a rapid-onset depolarization corresponding to a weakly voltage-dependent inward current showing little or no change in conductance. In addition, 30% of the neurons displayed both types of responses. Finally, 18% of the neurons were unresponsive to hydrogen sulfide. The outward current induced by hydrogen sulfide was demonstrated to be caused by an elevated conductance to potassium, whereas the hydrogen sulfide-induced inward current is carried by calcium ions. However, the mechanism of calcium ion entry is not clear.

Hydrogen sulfide was shown to inhibit, in a concentration-dependent fashion, all components of the complex evoked synaptic responses of the dorsal raphe serotonergic neurons (Kombian et al. 1993). This effect was rapid and reversible, and involved both pre- and postsynaptic mechanisms. Similar effects of hydrogen sulfide on brain hippocampal CA1 neurons have been reported. The electrophysiological effects of hydrogen sulfide are comparable to those elicited by anoxia. The neuronal action of hydrogen sulfide may involve an interaction with free thiols and disulfide bonds present in most membrane proteins. Collectively, the electrophysiology data suggest a possible role of the effects of hydrogen sulfide on synaptic and membrane properties of the dorsal raphe serotonergic neurons of the brain stem in the cessation of respiratory drive following acute hydrogen sulfide exposure.

Inhibition of monoamine oxidase has been proposed as a possible mechanism underlying the hydrogen sulfide–mediated disruption of neurotransmission in brain stem nuclei controlling respiration (Warenycia et al. 1989a). Administration of sodium hydrosulfide, an alkali salt of hydrogen sulfide, has been shown to increase brain catecholamine and serotonin levels in rats. It has also been suggested that persulfide formation resulting from sulfide interaction with tissue cystine and cystinyl peptides may underlie some aspects of hydrogen sulfide neurotoxicity, including inhibition of monoamine oxidase (Warenycia et al. 1990).

3.5.3 Animal-to-Human Extrapolations

The toxicokinetic disposition of hydrogen sulfide in humans is not understood. However, available toxicity and toxicokinetic data indicate that hydrogen sulfide can be readily absorbed through the lung and, to a lesser and clinically irrelevant extent, through the gastrointestinal tract and skin. Although the metabolism of hydrogen sulfide has been characterized in animals, there are limited data to suggest that the metabolism of hydrogen sulfide may be in part similar in humans. For instance, human data indicate that hydrogen sulfide is oxidized to sulfate and thiosulfate and excreted in the urine. Neurotoxicity induced by hydrogen sulfide has been observed in experimental animals and humans.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or

elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were identified on the potential for hydrogen sulfide to disrupt the function of the neuron-endocrine axis.

3.7 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 resulting from 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 6.6, 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 prenatal and postnatal life, and a particular structure or 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 (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. 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 (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends 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 newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining 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, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Although there is a fair amount of data on the toxicity of hydrogen sulfide in humans, there is very little information to judge the impacts of exposure to hydrogen sulfide in infants and children. In adults, exposure to high concentrations of hydrogen sulfide can result in unconsciousness followed by an apparent complete recovery. At lower exposure levels, exposure to hydrogen sulfide can result in less severe neurological (e.g., incoordination, poor memory, olfactory impairment) and respiratory symptoms. Animal data suggest that the respiratory tract, particularly the nasal olfactory epithelium, may be the most sensitive target following hydrogen sulfide exposure. It is likely that similar toxicological effects will be seen in children.

Available human data suggest that maternal or paternal exposure may increase the risk of spontaneous abortions (Hemminki and Niemi 1982; Xu et al. 1998). However, co-exposure to other chemicals precludes establishing a causal relationship from these data. Animal studies did not find structural anomalies, developmental delays, or alterations in performance on developmental neurobehavioral tests

or brain histology in the offspring of animals exposed to 80 ppm or lower hydrogen sulfide during gestation (Dorman et al. 2000; Hayden et al. 1990a; Saillenfait et al. 1989). In contrast, alterations in Purkinje cells (Hannah et al. 1990), brain amino acid levels (Hannah et al. 1989), and neurotransmitter levels (Skrajny et al. 1992) have been observed in rat offspring exposed to low levels (20–75 ppm) of hydrogen sulfide during gestation. However, the toxicological significance of these alterations in the absence of alterations in neurobehavioral performance is not known.

3.8 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, 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 hydrogen sulfide are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., deoxyribonucleic acid adducts). Biomarkers of effects caused by hydrogen sulfide are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Hydrogen Sulfide

The most frequently used biomarker of hydrogen sulfide exposure is urinary thiosullfate levels (Milby and Baselt 1999). Thiosulfate is an oxidation product of hydrogen sulfide metabolism and is not specific to hydrogen sulfide metabolism. Ingestion of food or water with a high sulfur content can also increase urinary thiosulfate concentrations (Milby and Baselt 1999). An increase in urinary thiosulfate levels were observed in individuals exposed to 8, 18, or 30 ppm hydrogen sulfide for 30–45 minutes (Kangas and Savolainen 1987). The urinary thiosulfate levels peaked approximately 15 hours after exposure. In a subject exposed to 18 ppm for 30 minutes, the peak urinary thiosulfate concentration at 15 hours was 30 µmol/mmol creatinine; 17 hours after exposure, the urinary thiosulfate levels were similar to non-exposed individuals (mean concentration of 2.9 µmol/mmol creatinine). A quantitative relationship between hydrogen sulfide exposure levels and urinary thiosulfate levels has not been established.

Measurement of blood sulfide levels has also been proposed as a biomarker of exposure (Jappinen and Tenhunen 1990). This has limited clinical value because the blood samples must be collected within 2 hours of exposure (Jappinen and Tenhunen 1990). As with urinary thiosulate levels, a relationship between airborne hydrogen sulfide levels and blood sulfide levels has not been established.

Jappinen and Tenhunen (1990) also investigated the use of alterations in blood heme metabolism as a possible biomarker of hydrogen sulfide exposure. The activities of the enzymes of heme synthesis, i.e., delta-aminolaevulinic acid synthase (ALA-S) and heme synthase, were examined in 21 cases of acute hydrogen sulfide toxicity in Finnish pulp mill and oil refinery workers exposed to 20–200 ppm hydrogen sulfide for periods ranging from approximately 1 minute up to 3.5 hours. Several subjects lost consciousness for up to 3 minutes. Activities of delta-aminolaevulinic acid synthase and heme synthase were decreased after exposure to hydrogen sulfide. However, the changes in heme metabolism are not

specific for hydrogen sulfide, and other sulfur-containing compounds, such as methyl mercaptan, can produce similar effects.

3.8.2 Biomarkers Used to Characterize Effects Caused by Hydrogen Sulfide

Hydrogen sulfide-specific biomarkers of effect have not been identified. Potential biomarkers for neurological effects of hydrogen sulfide include indices of cortical, hippocampal, brain stem, basal ganglia, and diencephalon dysfunction. An oil-field worker who became unconscious following exposure to hydrogen sulfide had a diminished vibration sense, delayed visual reaction times, abnormal balance with eyes closed, slow blink reflex latency, impaired verbal and visual recall, and decreased cognitive performance (Kilburn 1993). Cortical function tests revealed deficits in verbal abstraction, attention, and short-term retention in a hydrogen sulfide-poisoned patient (Stine et al. 1976). A 5-year neuro-psychological re-examination of patients who lost consciousness after hydrogen sulfide exposure revealed neurological impairment (Tvedt et al. 1991b); memory and motor function were most affected. Such neurological effects are not specific for hydrogen sulfide and could indicate exposure to other neurotoxic substances.

3.9 INTERACTIONS WITH OTHER CHEMICALS

In a group of Belgian viscose rayon workers exposed to 0.14 or 6.4 ppm of hydrogen sulfide and at least 26 mg/m^3 of carbon disulfide, the incidence of eye irritation was significantly higher in all hydrogen sulfide-exposed workers than in unexposed controls (Vanhoorne et al. 1995). Control for confounders such as cigarette smoke was not performed (Vanhoorne et al. 1995). Simultaneous exposure of Sprague-Dawley rats to 500 ppm of carbon disulfide and 50 ppm of hydrogen sulfide 5 days/week, for 25 weeks, had no interactive effect on sensory tail nerve conduction velocities (SNCV) or motor tail nerve conduction velocities (MNCV) (Gagnaire et al. 1986). Additionally, the amount of 2-thio-thiazo-lidine-4-carboxylic acid, a urinary metabolite of carbon disulfide excreted in urine after exposure to carbon disulfide, was unaffected by hydrogen sulfide exposure (Gagnaire et al. 1986). In a series of reproductive and developmental studies in which albino rats were exposed to hydrogen sulfide and carbon disulfide, both pre- and postimplantational lethality as well as developmental anomalies of the genito-urinary and skeletal systems were reported (Barilyak et al. 1975). However, in some cases, these effects occurred in conjunction with maternal toxicity. It is not clear whether the reported concentration

(10 mg/m^3) to which the animals were exposed includes both hydrogen sulfide and carbon disulfide or represents individual concentrations of each chemical.

There appears to be some evidence that ethanol can increase the effects of hydrogen sulfide. In six cases, less hydrogen sulfide was needed for toxic effects to be observed when workers had consumed alcohol 16–24 hours earlier (Poda 1966).

Much of the occupational data on hydrogen sulfide comes from studies of pulp and paper mill workers who were exposed to other compounds in addition to hydrogen sulfide. An increase in chronic or recurrent headache was noted in Finnish pulp workers who were exposed simultaneously to hydrogen sulfide, methyl mercaptans, and sulfur dioxide (Kangas et al. 1984). Peak concentrations of the chemicals, up to 20 ppm hydrogen sulfide, were believed to be responsible for the occurrence of the symptoms, rather than the lower mean concentrations. A respiratory survey of almost 2,000 Canadian pulp and paper mill workers did not show any increases in the prevalence of respiratory symptoms or pulmonary function abnormalities among exposed workers (Chan-Yeung et al. 1980). Mean exposure concentrations of toxicants measured in this study were 0.05 ppm hydrogen sulfide, 0.3 ppm sulfur dioxide, 8.3 ppm carbon monoxide, 0.8 ppm total particulates, and <0.05 ppm chlorine.

No changes in body weight or microscopic changes in respiratory tract, eye, or visceral organs were noted in crossbred pigs inhaling 2 ppm of hydrogen sulfide and 50 ppm of ammonia continuously for 19 days when compared to controls (Curtis et al. 1975). The toxicity of hydrogen sulfide after dermal exposure was found to be enhanced by dermal exposure to ammonia (Laug and Draize 1942).

Male Wistar rats were administered 330 or 660 mg/kg of ethanol intraperitoneally 30 minutes before being exposed to 800 ppm of hydrogen sulfide for a maximum of 20 minutes, which was a potentially fatal hydrogen sulfide exposure (Beck et al. 1979). Mean times to unconsciousness in animals that were exposed to hydrogen sulfide with ethanol pretreatment at either of these dose levels were approximately 35% less than times to unconsciousness without ethanol pretreatment (Beck et al. 1979). The clinical relevance of these findings, which used potentially fatal doses of both ethanol and hydrogen sulfide, is unclear.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to hydrogen sulfide than will most persons exposed to the same level of hydrogen sulfide 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 result in reduced detoxification or excretion of hydrogen sulfide, or compromised function of organs affected by hydrogen sulfide. Populations who are at greater risk due to their unusually high exposure to hydrogen sulfide are discussed in Section 6.7, Populations with Potentially High Exposures.

Some asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes had changes in pulmonary function tests indicative of bronchial obstruction, although the exposed group as a whole did not show a statistically significant change in these parameters (Jappinen et al. 1990). Asthmatics have also been found to have a worsening of their condition upon exposure to odors (Shim and Williams 1986). Although this has not been tested with exposure to hydrogen sulfide, it might be reasonably anticipated due to the malodorous quality of hydrogen sulfide gas. These findings suggest that some asthmatics may be more sensitive to hydrogen sulfide than the general population.

Evidence from a number of studies suggests that hydrogen sulfide, endogenously produced by bacteria in the digestive tract, may play a role in the etiology of ulcerative colitis (Babidge et al. 1998; Pitcher and Cummings 1996; Roediger et al. 1997). It is unclear whether patients are affected due to the excess production of hydrogen sulfide or the inability to detoxify it as effectively as controls. Irrespective of mechanism, it seems likely that individuals already suffering from hydrogen sulfide-associated toxicity will be at higher risk from further hydrogen sulfide exposures. Ulcerative colitis is usually found in adults, so children are less susceptible.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to hydrogen sulfide. 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 hydrogen sulfide. 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 hydrogen sulfide:

Agency for Toxic Substances and Disease Registry. 1994. Hydrogen sulfide. Managing hazardous materials incidents. Volume III. Medical management guidelines for acute chemical exposures. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Ellenhorn MJ. 1997. Hydrogen sulfide. In: Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd edition. Baltimore, MD: Williams and Wilkins, 1489-1493.

Hall AH. 1996. Systemic asphyxiants. In: Rippe JM, Irwin RS, Fink MP, et al. eds. Intensive care medicine. 3rd edition. Boston, MA: Little, Brown, and Company, 1706-1718.

There is no widely accepted antidote for hydrogen sulfide poisoning. Treatment consists of supportive measures such as evaluating and supporting airway, breathing, and circulation (Agency for Toxic Substances and Disease Registry 1994). A number of case reports of individuals exposed to high concentrations of hydrogen sulfide resulting in unconsciousness suggest that administration of sodium nitrite and/or amyl nitrite may be an effective antidote for hydrogen sulfide poisoning (Hall 1996; Hall and Rumack 1997; Hoidal et al. 1986; Stine et al. 1976). The nitrite induces the formation of methemoglobin, which has a higher affinity for hydrogen sulfide than does cytochrome oxidase. Hyperbaric oxygen therapy is controversial, but it may be effective for patients not treated successfully by other measures (Agency for Toxic Substances and Disease Registry 1994).

There are no pediatric-specific methods for reducing toxic effects.

3.11.1 Reducing Peak Absorption Following Exposure

There are no specific methods available to reduce the absorption of hydrogen sulfide following exposure. Supportive treatment includes artificial respiration if respiration is depressed; administration of oxygen; and standard medical treatment for eye irritation, pulmonary edema, seizures, and hypotension (Sorokin 1993).

3.11.2 Reducing Body Burden

There are no known methods for reducing the body burden of hydrogen sulfide, although adopting a diet low in sulfur-containing, exogenously acquired foods, e.g., milk and cheese, has been shown to reduce the endogenous production of hydrogen sulfide (Roediger et al. 1997).

The major metabolic pathway of hydrogen sulfide is the oxidation of the sulfide to sulfate in the liver (Beauchamp et al. 1984). Methylation also serves as a detoxification route. Hydrogen sulfide is excreted primarily as sulfate (either as free sulfate or as thiosulfate) in the urine.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hydrogen sulfide inhibits mitochondrial cytochrome oxidase, resulting in disruption of the electron transport chain and impairing oxidative metabolism. Nervous and cardiac tissues, which have the highest oxygen demand (e.g., brain and heart), are especially sensitive to disruption of oxidative metabolism (Ammann 1986; Hall 1996).

Nitrites such as amyl and sodium nitrites have been used in the treatment of hydrogen sulfide poisoning, and the mechanism of therapeutic action may involve the prevention or reversal of cytochrome oxidase inhibition (Ellenhorn 1997; Hall 1996; Hoidal et al. 1986; Osbern and Crapo 1981; Reiffenstein et al. 1992). It has been postulated that nitrites induce methemoglobin, which inactivates sulfide, thereby preventing cytochrome oxidase inhibition and reactivating aerobic respiration (Ellenhorn 1997; Hall 1996). There is antidotal evidence to suggest that this is an effective treatment in cases of exposure to high concentrations of hydrogen sulfide (Hall 1996; Hall and Rumack 1997; Hoidal et al. 1986; Stine et al. 1976).

Oxygen treatment may be used after hydrogen sulfide poisoning, although its use is somewhat controversial (Ellenhorn 1997; Ravizza et al. 1982). Smith et al. (1976) found that oxygen was not useful as an antidote to hydrogen sulfide poisoning in mice. High intracellular oxygen pressure may result in nonenzymatic oxidation of cytochrome oxidase, and oxygen may release sulfide from cytochrome oxidase binding by a concentration effect (Ravizza et al. 1982). Hyperbaric oxygen therapy has been suggested for cases not responding to supportive care and nitrite treatment, but its clinical efficacy has not yet been determined (Ellenhorn 1997; Hall 1996).

In one case report (Schneider et al. 1998) where an individual suffered long-term (4 years later) neuropsychological sequelae from a "knock-down" exposure to hydrogen sulfide, treatment with two drugs, Ritalin and Cyclert, partially alleviated some of the observed deficits in cognitive function and general cognition; these drugs enhance dopaminergic functioning. However, more examples of the efficacy of this treatment are required.

3.12 ADEQUACY OF THE DATABASE

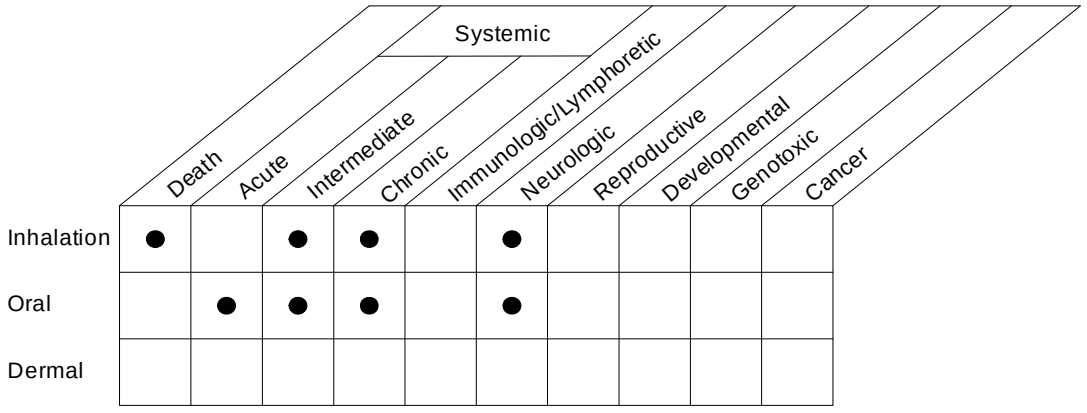
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hydrogen sulfide is available. Where adequate information 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 hydrogen sulfide.

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.

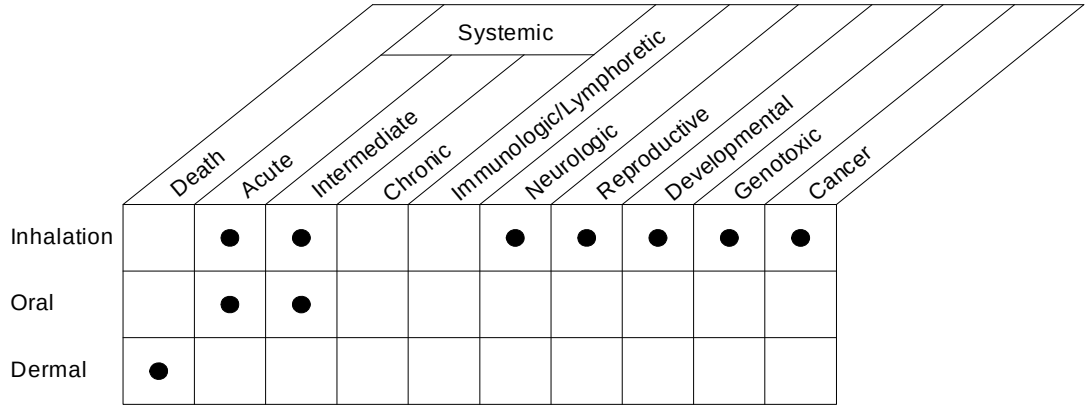
3.12.1 Existing Information on Health Effects of Hydrogen Sulfide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hydrogen sulfide are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of hydrogen sulfide. 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* (Agency for Toxic Substances and Disease Registry 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.

Figure 3-4. Existing Information on Health Effects of Hydrogen Sulfide



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are numerous case reports of human fatalities (Adelson and Sunshine 1966; Allyn 1931; Breysse 1961; Campanya et al. 1989; Deng and Chang 1987; Freireich 1946; Hagley and South; Morse et al. 1981; Osbern and Crapo 1981; Parra et al. 1991) or survivors who developed immediate as well as delayed neurological effects (Deng and Chang 1987; Kilburn 1993, 1997; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Schneider et al. 1998; Spolyar 1951) following acute-duration hydrogen sulfide inhalation exposure. Estimates of exposure concentrations were not often reported in these studies. Cardiac arrhythmia has also been reported in workers exposed to hydrogen sulfide (Krekel 1964). Experimental exposure studies in which subjects were exposed to hydrogen sulfide for 15–30 minutes did not identify any respiratory or cardiovascular effects in healthy subjects at 5 or 10 ppm (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a). Pulmonary function tests were normal in workers exposed to up to 10 ppm hydrogen sulfide (Jappinen et al. 1990). Evidence of bronchial obstruction was observed in 2 of 10 asthmatics exposed to 2 ppm of hydrogen sulfide, although the group as a whole had no significant change in these parameters (Jappinen et al. 1990). Additionally, studies are needed to assess whether asthmatic subjects are a sensitive subpopulation. Because hydrogen sulfide gas is an eye irritant (Ahlborg 1951; Luck and Kaye 1989), such studies should also monitor ocular effects. Additional studies of the delayed consequences of acute exposures are also needed.

Acute-duration inhalation studies of hydrogen sulfide in animals have reported death (Beck et al. 1979; Khan et al. 1990; Lopez et al. 1989; Nagata et al. 1990; Prior et al. 1988, 1990; Smith and Gosselin 1964; Tansy et al. 1981), respiratory (Brenneman et al. 2002; Green et al. 1991; Khan et al. 1990; Kohno et al. 1991; Lopez et al. 1987, 1988a, 1988b; Prior et al. 1990), cardiovascular (Higuchi and Fukamachi 1977; Kohno et al. 1991; Kosmider et al. 1967), immunological/lymphoreticular (Khan et al. 1991), and neurological effects (Beck et al. 1979; Haider et al. 1980; Higuchi and Fukamachi 1977; Kosmider et al. 1967; Lopez et al. 1988b; Struve et al. 2001). Additional acute-duration inhalation animal studies would be useful to further define any direct cardiovascular effects of hydrogen sulfide as opposed to those due to hypoxia. The available data on the acute toxicity of inhaled hydrogen sulfide were sufficient for derivation of an acute-duration inhalation MRL.

Data are not sufficient for the development of an acute-duration oral MRL. The only oral study of hydrogen sulfide is a study in which a diarrheic digestive disorder was observed in pigs fed hydrogen sulfide at 15 mg/kg/day for "a few days" (Wetterau et al. 1964). Acute dermal exposure of animals has

resulted in death (Laug and Draize 1942). In addition to a lack of route-specific toxicity data, insufficient pharmacokinetic data are available to support the identification of target organs across routes of exposure. However, although oral and dermal data regarding the effects of hydrogen sulfide are very limited, human exposure would be expected to be principally by inhalation.

Intermediate-Duration Exposure. Intermediate-duration studies in humans are fairly limited and virtually all are complicated by exposures to other chemicals as well as rarely being accompanied with adequate exposure assessment. Additional epidemiologic studies, particularly prospective or case-control, of populations exposed environmentally to various levels of hydrogen sulfide (where other pollutants are monitored and ideally, do not vary) are needed.

A series of 90-day inhalation studies in rats (CIIT 1983b, 1983c) reported significantly decreased body weights in Sprague-Dawley female rats at 80 ppm, but not in male Sprague-Dawley (CIIT 1983c) nor in either sex of F-344 rats (CIIT 1983b). Although CIIT (1983b, 1983c) did not report increases in the occurrence histological lesions, a re-examination of the histological slides from this study (Dorman et al. 2004) found increases in the incidence of nasal (olfactory neuron loss) and lung (bronchiolar epithelial hypertrophy and hyperplasia) lesions at 30 ppm and higher. In a companion study with $B6C3F_1$ mice, a significant increase in the incidence of inflammation of the nasal mucosa was observed at a dose level of 80 ppm but not at 30.5 ppm. Brenneman et al. (2000) identified a NOAEL and LOAEL for nasal effects (loss of olfactory neurons) in Sprague-Dawley rats exposed to 10 and 30 ppm, respectively, for 10 weeks. This study was used as the basis of an intermediate-duration inhalation MRL for hydrogen sulfide.

No histopathological effects were found in respiratory tract tissues or organs when pigs were exposed to 8.5 ppm hydrogen sulfide continuously for 17 days (Curtis et al. 1975). Additional effects reported in rats following inhalation exposure to hydrogen sulfide include increased glucose in lactating rats (Hayden et al. 1990a), increased liver cholesterol in female rats exposed during gestation and lactation (Hayden et al. 1990b), and weight loss in pregnant rats (Saillenfait et al. 1989).

The only oral study of hydrogen sulfide is a study in pigs in which decreased body weights were observed in pigs fed hydrogen sulfide in the diet at 6.7 mg/kg/day for 105 days (Wetterau et al. 1964). No effects were observed at a dose of 3.1 mg/kg/day. However, because this study lacks details and there are no supporting data, no intermediate-duration MRL was derived. Additional intermediate-duration oral studies of hydrogen sulfide are needed to provide support for this study.

No intermediate-duration dermal studies of hydrogen sulfide were identified. As significant human dermal exposure to hydrogen sulfide is unlikely, dermal exposure studies should not be a high priority. However, no pharmacokinetic data are available that might support the identification of target organs across routes of exposures in the absence of route-specific toxicity data.

Chronic-Duration Exposure and Cancer. A study of workers exposed to hydrogen sulfide at concentrations that often exceeded 20 ppm reported slight irritation of the mucous membranes, fatigue, loss of appetite, headache, irritability, poor memory, and dizziness (Ahlborg 1951). Pulp industry workers exposed to 8-hour TWA concentrations of 0.05–5.2 ppm hydrogen sulfide had no signs of clinical anemia but did show decreases in ALA-S, Heme-S, and ALA dehydratase activities, as well as erythrocyte protoporphyrin (Tenhunen et al. 1983). This study was confounded by workers' exposure to other compounds such as methyl mercaptan and dimethylsulfide, inadequately described controls, and an absence of statistical analysis. A study of persons living near a paper mill who were exposed to hydrogen sulfide showed increased eye irritation and some respiratory effects compared to nonexposed individuals; however, they were also exposed to methyl mercaptan and sulfur dioxide (Jappinen et al. 1990). There was no increase in cancer incidence noted in a residential cohort study of persons living downwind from natural gas refineries (Schechter et al. 1989), but an increased risk of nasal cancers was found in a population residing in a location of high geothermal activity (Bates et al. 1998).

Additional chronic-duration studies of hydrogen sulfide, including studies of the carcinogenic potential of hydrogen sulfide in humans and animals by any route of exposure, have not been performed. Follow-up epidemiological studies of populations environmentally exposed to hydrogen sulfide due to proximity of pulp mills, sour gas plants, or geothermal energy sources are needed, but only if they are accompanied by adequate exposure measurements. As limited genotoxicity studies suggest that hydrogen sulfide is unlikely to be a carcinogen, lifetime carcinogenicity studies in animals should not be a high priority. In the absence of route-specific toxicity data and route-specific pharmacokinetic data, it is not possible to identify target organs across routes of exposure.

Genotoxicity. No mutagenicity was observed in Ames assays using *Salmonella typhimurium* strains TA97, TA98, and TA100, either with or without S9 liver fractions from male Syrian golden hamsters or Sprague-Dawley rats (EPA 1984). Specific concentrations of hydrogen sulfide gas were limited because of its solubility in ethanol, which was the test solvent. The highest dose that could be obtained was 1,750 μg/plate. Other studies using hydrogen sulfide in the gaseous state would be useful for testing higher doses.

Reproductive Toxicity. The findings in two studies (Hemminki and Niemi 1982; Xu et al. 1998) that exposures to hydrogen sulfide are associated with an increased risk of spontaneous abortion warrants further investigation. A well-designed case-control study is needed in which exposure is well characterized in order to ascertain whether this is indeed an effect of concern or merely an anomaly. Additional epidemiologic studies of other reproductive effects would also be useful. No treatment-related histopathological changes were found in the male or female reproductive organs of rats (CIIT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days or in rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 60–70 days (Dorman et al. 2000). The Dorman et al. (2000) study also found no exposure-related alterations in fertility, late resorptions or stillbirths, litter size, or length of gestation. A multilitter or multigeneration study in several animal species after exposure to hydrogen sulfide by inhalation is needed to further evaluate the reproductive potential of hydrogen sulfide.

Developmental Toxicity. No studies were located regarding developmental effects in humans following hydrogen sulfide exposure.

Developmental effects were not observed in rats exposed to hydrogen sulfide by inhalation at concentrations that resulted in maternal body weight loss (Saillenfait et al. 1989), increased maternal blood glucose levels (Hayden et al. 1990a), or increased cholesterol content of the maternal liver (Hayden et al. 1990b). Purkinje cell path length in offspring of exposed rats was increased compared to controls (Hannah and Roth 1991). Changes in amino acid levels (Hannah et al. 1989, 1990) and serotonin and epinephrine levels (Skrajny et al. 1992) in the brain were found in the offspring of rats exposed by inhalation to hydrogen sulfide during gestation. No alterations in performance on neurobehavioral tests were observed in the offspring of rats exposed to up to 80 ppm 6 hours/day, 7 days/week during gestation and lactation (the pups were also exposed on postnatal days 5–18) (Dorman et al. 2000). Studies regarding the developmental toxicity of hydrogen sulfide following oral or dermal exposure were not located.

Immunotoxicity. Immunological effects infrequently observed after human hydrogen sulfide exposure appear to result from infection due to the aspiration or ingestion of manure or vomit (Osbern and Crapo 1981). No treatment-related histopathological changes were found in the spleen or lymph nodes of rats (CIIT 1983b, 1983c) or mice (CIIT 1983a) exposed to hydrogen sulfide for 6 hours/day, 5 days/week, for 90 days. Although the number of pulmonary alveolar macrophage cells was not

influenced by hydrogen sulfide exposure, the number of viable cells was significantly decreased with exposure to 400 ppm (Khan et al. 1991). When pulmonary alveolar macrophage cells were treated with Zymosan to stimulate respiration rates, there was no stimulation of respiration in cells from animals exposed to 200 or 400 ppm of hydrogen sulfide for 4 hours (Khan et al. 1991). Immunological effects have not been studied in humans or animals following oral or dermal exposure to hydrogen sulfide.

Additional studies of immune function in animals exposed to hydrogen sulfide by inhalation are needed. A bacterial and/or viral challenge study would be especially useful to determine whether exposure to hydrogen sulfide increases susceptibility to infection.

Neurotoxicity. The nervous system is a target organ for hydrogen sulfide. Effects of acute inhalation exposure in humans include nausea, headaches, delirium, disturbed equilibrium, poor memory, loss of consciousness, tremors, and convulsions (Arnold et al. 1985; Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Acute effects observed in animals include fatigue, somnolence (Haider et al. 1980), and loss of consciousness (Kosmider et al. 1967). Limited data from chronically exposed workers indicate that loss of appetite, fatigue, poor memory, dizziness, and irritability may result (Ahlborg 1951; Krekel 1964). Studies in rats have shown decreases in performance of discriminated avoidance tasks after exposure to hydrogen sulfide (Higuchi and Fukamachi 1977). The potential neurotoxicity of hydrogen sulfide following oral or dermal exposures has not been characterized. The transplacental neurological effects of hydrogen sulfide exposure are unknown. There is no reason to suspect that the neurotoxic effects observed after hydrogen sulfide exposure are species-specific, and insufficient data are available to determine whether effects are route-specific. Well-designed studies investigating neurotoxic effects in animals following oral or dermal exposure and chronic neurotoxic effects after inhalation exposure are needed to determine the effects that might be seen in exposed humans. Additionally, there is antidotal evidence that some individuals experience permanent or persistent neurological symptoms, such as memory loss, after acute exposures to high concentrations of hydrogen sulfide. Studies are needed to confirm these reports and determine if acute exposure to hydrogen sulfide can result in permanent neurological damage.

Epidemiological and Human Dosimetry Studies. Published reviews have addressed the duration of exposure and concentrations of hydrogen sulfide resulting in death and serious effects in humans (Beauchamp et al. 1984; EPA 1978; NIOSH 1977a; WHO 1981). The limited chronic-duration epidemiological studies (Ahlborg 1951; Jappinen et al. 1990; Schechter et al. 1989; Tenhunen et al. 1983) have identified approximate exposure concentrations, but exposure assessment was not sufficient to

divide the study population into more than one exposure group. Epidemiology studies examining the potential effects of chronic inhalation exposure to various hydrogen sulfide concentrations are needed. There are known populations that have unusually high exposure to hydrogen sulfide.

Biomarkers of Exposure and Effect.

Exposure. Both blood sulfide concentrations (Jappinen and Tenhunen 1990) and urinary thiosulfate concentrations (Kage et al. 1992; Kangas and Savolainen 1987) have been proposed as indicators of hydrogen sulfide exposure. Obtaining background levels of blood sulfide in a population should not be problematic, although blood samples to determine sulfide concentrations must be obtained within 2 hours of exposure to hydrogen sulfide. Similarly, urinary thiosulfate levels can be obtained for the background population. Further study is needed to correlate airborne exposure concentrations with blood sulfide and thiosulfate levels. Additional alterations in heme synthesis enzymes (delta-aminolaevulinic acid synthase and heme synthase) have been proposed as possible biomarkers of exposure (Jappinen and Tenhunen 1990). These effects are not specific for hydrogen sulfide, and further study is needed to correlate these effects with blood sulfide and urinary thiosulfate levels.

Effect. No hydrogen-sulfide-specific biomarkers of effect have been identified. Neurological indices are also used as biomarkers of effect for hydrogen sulfide (Gaitonde et al. 1987; Kilburn 1993; Stine et al. 1976; Tvedt et al. 1991b). It is unlikely that a hydrogen-sulfide-specific biomarker of effect will be identified based on nonspecific effects that have been observed in humans and animals exposed to hydrogen sulfide and the mechanistic similarity between cyanide and hydrogen sulfide. Additional data are needed to identify a collection of symptoms that could reasonably characterize hydrogen sulfide exposure.

Absorption, Distribution, Metabolism, and Excretion. Hydrogen sulfide is absorbed through the lungs and can be absorbed in minor quantities through the gastrointestinal tract and intact skin (Kohno et al. 1991; Laug and Draize 1942; Wetterau et al. 1964). Hydrogen sulfide is also produced endogenously in many tissues (e.g., liver, kidney, and heart) as a break-down product of cysteine metabolism. Thus, hydrogen sulfide is widely distributed in the body. Sulfides have been found in the heart, liver, blood, brain, lungs, spleen, and kidneys of humans who died after accidental inhalation exposure (Kohno et al. 1991). However, there are no studies that have tracked the quantitative absorption or endogenous production of hydrogen sulfide nor quantified the differences in its distribution in the

various tissues to follow absorption of an external dose. No data are available on distribution after oral or dermal exposure to hydrogen sulfide.

Hydrogen sulfide is metabolized through three pathways: oxidation, methylation, and reactions with metalloproteins or disulfide-containing proteins (Beauchamp et al. 1984). Although the major metabolic pathway for detoxification is oxidation of the sulfide to sulfate in the liver, methylation also serves to detoxify hydrogen sulfide (EPA 1987a; Weisiger and Jakoby 1979). The major oxidation product of hydrogen sulfide is thiosulfate, which is then converted to sulfate and excreted in the urine (Bartholomew et al. 1980; Kage et al. 1992; Kangas and Savolainen 1987). The primary location for the oxidation reaction is the liver (Bartholomew et al. 1980).

The qualitative data on the absorption, distribution, metabolism, and excretion of hydrogen sulfide in humans and animals are well known; quantitative data are generally lacking. Additional studies in animals that provide quantitative toxicokinetic data are needed.

Comparative Toxicokinetics. PBPK models have not been developed to compare the toxicokinetics of hydrogen sulfide in humans and animals. Studies providing quantitative data necessary to develop PBPK models would be useful.

Methods for Reducing Toxic Effects. Other than removing the subject from exposure, there is no specific method to reduce the absorption of hydrogen sulfide. There are no known methods for reducing the body burden of hydrogen sulfide, although reducing the intake of sulfhydryl-containing amino acids has been shown to reduce endogenous production. Amyl and sodium nitrites have been used as antidotes for hydrogen sulfide. Oxygen treatment, which may result in nonenzymatic oxidation of cytochrome oxidase, may also be used in the treatment of hydrogen sulfide poisoning (Hall 1996; Ravizza et al. 1982).

There is a need to develop an antidote for hydrogen sulfide poisoning, especially since it has a high knock-down potency. Additional research into the safe use of oxygen as an antidote for hydrogen sulfide poisoning is needed. Studies examining methods to enhance the oxidation or methylation of hydrogen sulfide to increase the elimination might also be useful. Further studies of the efficacy of drugs such as Retalin and Cyclert to treat the long-term neuropsychological effects of a knock-down exposure are needed.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There is only limited information available by which to assess the potential toxicity of hydrogen sulfide to children and infants. Several case reports suggest that adolescents respond much like adults to high dose acute exposures (Allyn 1931; Hagley and South 1983; Morse et al. 1981), but there is no information with which to determine whether the long-term consequences of such exposures differ for adolescents versus adults, nor is there any information on the effects of hydrogen sulfide exposures in children and very little information on infants. Several developmental toxicity studies indicated that the exposure of pregnant rats and their pups to hydrogen sulfide resulted in structural and biochemical changes in the brain (Hannah and Roth 1991; Hannah et al. 1989, 1991). Subsequent work showed that many of the biochemical changes were transient; however, no studies were found that evaluated the behavioral consequences of these changes. Thus, a variety of studies are needed in order to determine whether children and infants are at risk from neurological deficits following hydrogen sulfide exposures *in utero* or during childhood and adolescence; information from such studies would also be useful in order to determine whether children are more sensitive to hydrogen sulfide exposure.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

A limited number of ongoing studies, designed to investigate mechanisms of hydrogen sulfide production in the digestive tract and potential health concerns, were identified in the Federal Research in Progress database (FEDRIP 2004). These studies are summarized below.

Dr. L. Chu, from the University of Texas Health Science Center, has designed studies to elucidate enzymatic mechanisms involved in hydrogen sulfide production by the oral bacterium, *Treponema denticola*, and to characterize the effects the hydrogen sulfide-induced effects on host inflammatory/ immune functions.

Dr. M. Levitt, from the Department of Veterans Affairs Medical Center in Minneapolis, Minnesota, has designed experiments in rats to investigate toxicity following the intestinal infusion of sodium sulfide.

Dr. Levitt has also designed experiments to investigate the metabolic fate of hydrogen sulfide and other sulfur-containing compounds in the rat.

Dr. Fiedler and associates are investigating the neurological toxicity of hydrogen sulfide following low-level exposure.