

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO HYDROGEN SULFIDE AND CARBONYL SULFIDE IN THE UNITED STATES

*Hydrogen Sulfide.* Hydrogen sulfide (H<sub>2</sub>S) is a colorless gas with a characteristic odor of rotten eggs. It naturally occurs in the gases from volcanoes, sulfur springs, undersea vents, swamps, stagnant bodies of water, and in crude petroleum and natural gas. Additionally, bacteria, fungi, and actinomycetes release hydrogen sulfide during the decomposition of sulfur-containing proteins and by the direct reduction of sulfate (SO<sub>4</sub><sup>2-</sup>). Hydrogen sulfide is frequently encountered in various industries and may be released to the environment as a result of their operations. Some of these industries include natural gas production, municipal sewage pumping and treatment plants, landfilling, swine containment and manure handling, pulp and paper production, construction in wetlands, asphalt roofing, pelt processing, animal slaughter facilities, tanneries, petroleum refining, petrochemical synthesis, coke production plants, viscose rayon manufacture, sulfur production, iron smelting, and food processing.

Ambient air concentrations of hydrogen sulfide from natural sources range between 0.00011 and 0.00033ppm. Concentrations of hydrogen sulfide in urban areas are generally <0.001 ppm. Much higher levels (often exceeding 0.09 ppm) have been detected in communities living near natural sources of hydrogen sulfide or near industries releasing hydrogen sulfide.

Humans may be exposed to hydrogen sulfide from both its endogenous production and exogenous sources. Most endogenous production apparently results from the metabolism of sulfhydryl-containing amino acids (e.g., cysteine) by bacteria present in both the intestinal tract and the mouth; it is also produced via enzymatic pathways involving cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS), and β-mercaptopyruvate sulfurtransferase (MST) in coordination with cysteine aminotransferase (CAT) and via a nonenzymatic pathway involving the reduction of elemental sulfur. Hydrogen sulfide produced in the mouth is a component of bad breath (halitosis); concentrations of 0.001–0.1 ppm have been measured in mouth air. It is generated in the large intestine by the bacterial reduction of inorganic sulfate and sulfite, and by fermentation of sulfur-containing amino acids. It can compose up to 10% of intestinal gases. In flatus, hydrogen sulfide concentrations as high as 18 ppm were recorded in individuals on a normal diet. Approximately half of the 13 subjects produced measurable levels of hydrogen sulfide.

## 2. RELEVANCE TO PUBLIC HEALTH

Hydrogen sulfide is one of three currently recognized endogenously produced gaseous messenger molecules referred to as gasotransmitters; nitric oxide and carbon monoxide are the other two gasotransmitters. A number of physiological functions have been identified for endogenously-produced hydrogen sulfide. In the cardiovascular system, endogenous hydrogen sulfide has been shown to be involved in vasoregulation (vasorelaxation and vasodilation) and inhibition and stimulation of vascular smooth muscle cell proliferation. In the brain, hydrogen sulfide acts as a neuromodulator; physiological concentrations of hydrogen sulfide enhance the N-methyl-D-aspartate (NMDA) receptor mediated response and can facilitate the induction of hippocampal long-term potentiation. Hydrogen sulfide has also been shown to upregulate GABA<sub>B</sub> receptor expression and may also be involved in regulating the synaptic activity of glial cells, regulation of the hypothalamo-pituitary system, and modulation of pain perception. Additionally, there is some evidence to suggest a role of endogenous hydrogen sulfide in insulin release from pancreatic islet cells, inflammatory responses, airway smooth muscle restriction and relaxation, regulation of various gastrointestinal functions including motility control and inflammatory response, and renal tubular function including glomerular filtration rate and sodium reabsorption. The cellular and molecular mechanisms for endogenous hydrogen sulfide effects appear to involve activation of ion channels including ATP-sensitive potassium channels, calcium-sensitive potassium channels, and calcium channels; downregulation of cyclic adenosine monophosphate (cAMP); and downregulation of cyclic guanosine monophosphate (cGMP).

There is considerable individual variability in the odor threshold for hydrogen sulfide in humans; the thresholds can range from 0.0005 to 0.3 ppm. However, at concentrations of  $\geq 100$  ppm, individuals may not detect hydrogen sulfide odor due to olfactory paralysis.

***Carbonyl Sulfide.*** Like hydrogen sulfide, carbonyl sulfide (COS) is a colorless gas with the odor of rotten eggs, although it may be odorless when it is free from impurities. It is abundant in the troposphere and can enter the atmosphere from both natural and anthropogenic sources. Carbonyl sulfide is generated from wetlands, salt marshes, soil, oceans, deciduous and coniferous trees, and volcanic gases.

Anthropogenic sources of carbonyl sulfide include production as a chemical intermediate, burning of biomass, oxidation of carbon disulfide and dimethyl sulfide, aluminum production; combustion of coal, extraction of natural gas and petroleum crude oil, recovery of sulfur, combustion of garbage and plastics, manufacture of synthetic fibers, starch, and rubber, fish processing, and automobiles. Carbonyl sulfide has also been detected in “Chinese drywall” samples.

## 2. RELEVANCE TO PUBLIC HEALTH

Carbonyl sulfide has a long lifetime in the troposphere, ranging from 2 to 10 years. It may contribute to ozone depletion. While it can be found in water and soils, it generally exists as a gas in the atmosphere.

As carbonyl sulfide is a component of the global sulfur cycle and exists in the atmosphere at high concentrations, the general population may be exposed to carbonyl sulfide through inhalation of ambient air. Thus, humans are constantly exposed to low levels of carbonyl sulfide. Occupational exposure is primarily a result of its production and use as a chemical intermediate and its production as a byproduct in petroleum refining and coal distillation.

## 2.2 SUMMARY OF HEALTH EFFECTS

***Hydrogen Sulfide.*** The general population is primarily exposed to hydrogen sulfide via the inhalation route. Although oral and dermal absorption can also occur, these routes only contribute small amounts to the overall body burden. Information on the toxicity of hydrogen sulfide in humans comes from case reports, occupational studies, and community studies. Hydrogen sulfide tends to be a problem in communities located near certain types of industrial sites including pulp and paper mills, natural gas production, swine containment and manure handling, or geothermal power plants. The interpretation of community studies is often limited by exposure to other chemicals. The human data suggest that the respiratory tract and nervous system are the most sensitive targets of hydrogen sulfide toxicity. The most commonly reported nonlethal effect found in individuals acutely exposed to high concentrations of hydrogen sulfide is unconsciousness followed by apparent recovery, colloquially referred to as “knockdown”. In most cases, actual exposure concentrations and durations are not known; estimates suggest that the concentrations exceed 500 ppm and the durations are short, typically <1 hour. Although there is an apparent recovery, many individuals report permanent or persistent neurological effects including headaches, poor concentration ability and attention span, impaired short-term memory, and impaired motor function. Respiratory distress or arrest and pulmonary edema are also associated with exposure to very high concentrations of hydrogen sulfide; it is believed that these respiratory effects are secondary to central nervous system depression or due to tissue hypoxia. Cardiovascular effects (e.g., cardiac arrhythmia and tachycardia) have also been observed following an acute exposure to high concentrations of hydrogen sulfide.

Exposure to lower concentrations of hydrogen sulfide can result in less severe neurological and respiratory effects. Reported neurological effects include incoordination, poor memory, hallucinations, personality changes, and anosmia (loss of sense of smell); the respiratory effects include nasal symptoms,

## 2. RELEVANCE TO PUBLIC HEALTH

sore throat, cough, and dyspnea. Impaired lung function has also been observed in asthmatics acutely exposed to 2 ppm hydrogen sulfide; no alterations in lung function were observed in studies of non-asthmatic workers.

Animal studies confirm the human data suggesting that the respiratory tract and the nervous system are the most sensitive targets of hydrogen sulfide toxicity. As with humans, unconsciousness was observed in rats exposed to very high concentrations of hydrogen sulfide (800 ppm); central nervous system depression (as evidenced by lethargy) and pulmonary edema were observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours. Decreased performance in neurological testing has been observed in rats exposed to 80–200 ppm hydrogen sulfide for 5 days to 11 weeks. Damage to the nasal olfactory epithelium is also observed in rats exposed to lower levels of hydrogen sulfide for an acute or intermediate duration; the adverse effect levels are 80 ppm (3 hours/day for 5 days) and 30 ppm (6 hours/day, 7 days/week for 10 weeks) following acute- or intermediate-duration exposure, respectively.

Information on the toxicity of hydrogen sulfide following oral or dermal/ocular exposure is limited. Oral exposure data are limited to a single pig study examining the effects of hydrogen sulfide in feed. Observed effects included a diarrheic digestive disorder and decreased body weight gain. Exposure to hydrogen sulfide gas can result in a number of ocular effects including keratoconjunctivitis, punctate corneal erosion, blepharospasm, lacrimation, and photophobia in humans. A community exposure study found a concentration-related increase in the prevalence of eye symptoms in residents exposed to low (daily mean of total reduced sulfur <10  $\mu\text{g}/\text{m}^3$ ), medium (10–30  $\mu\text{g}/\text{m}^3$ ), or high (>30  $\mu\text{g}/\text{m}^3$ ) air levels. Although hydrogen sulfide was the primary constituent of the total reduced sulfur levels, other sulfur compounds, as well as other air pollutants, may have contributed to the eye irritation.

There are limited human data suggesting that maternal or paternal exposure to hydrogen sulfide can increase the risk of spontaneous abortion among rayon textile, paper products, or petrochemical workers (or their spouses). However, the subjects (or their spouses) were exposed to a number of other hazardous chemicals that may have contributed to the increased risk. No significant alterations in reproductive performance were observed in rats exposed to 10–80 ppm hydrogen sulfide for an intermediate duration. The available animal data suggest that hydrogen sulfide is not a developmental toxicant at concentrations of 80 ppm and lower. No structural anomalies, developmental delays, performance in developmental neurobehavioral tests, or alterations in brain histology were observed in a well-conducted rat study. Another study found alterations in Purkinje cell growth in the offspring of rats exposed to 20 or 50 ppm

## 2. RELEVANCE TO PUBLIC HEALTH

hydrogen sulfide during the gestation and lactation periods; the toxicological significance of this finding in the absence of alterations in neurobehavioral performance is not known.

There are limited data on the potential of hydrogen sulfide to induce cancer in humans. One study found significant increases in the risk of developing cancers of the trachea, bronchus, and lung among residents exposed to high levels of naturally occurring hydrogen sulfide. However, the authors noted that the elevated disease rates were consistent with exposure to high concentrations of hydrogen sulfide and mercury; the contribution of mercury to the overall respiratory tract cancer rates cannot be determined from these data. Another study did not find significant alterations in cancer incidences among residents living near natural gas refineries. The carcinogenicity of hydrogen sulfide has not been assessed in animal studies.

A greater detailed discussion of the hydrogen sulfide-induced respiratory effects and neurological effects follows. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information of these effects and other health effects.

**Respiratory Effects.** Exposure to very high concentrations of hydrogen sulfide can result in respiratory arrest and/or pulmonary edema. Numerous case reports suggest that these effects can occur after a brief exposure to hydrogen sulfide. Although the exact mechanism is not known, there is strong evidence to suggest that the rapid respiratory failure and possibly the pulmonary edema are secondary to the action of hydrogen sulfide on the respiratory center of the brain. There is also some evidence that the respiratory failure and pulmonary edema may be due to a dose-dependent inhibition of cytochrome oxidase in lung mitochondria, the terminal step in oxidative metabolism, resulting in tissue hypoxia. At low concentrations, hydrogen sulfide is a respiratory irritant. Residents living near industries emitting hydrogen sulfide, such as paper mills, hog operations, animal slaughter facilities, or tanneries, reported nasal symptoms, cough, or increased visits to the hospital emergency room due to respiratory symptoms (including asthma). In general, exposure to hydrogen sulfide has not resulted in significant alterations in lung function. No alterations in lung function were observed in workers chronically exposed to 1–11 ppm hydrogen sulfide. However, there is some evidence to suggest that asthmatics may be a sensitive subpopulation. No statistical alterations in lung function were observed in a group of 10 asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes (as compared with pre-exposure values). However, increased airway resistance and decreased specific airway conductance (suggestive of bronchial obstruction) were observed in 2 out of the 10 subjects.

## 2. RELEVANCE TO PUBLIC HEALTH

Although human data are useful in establishing the respiratory tract as a target of toxicity, concentration-response relationships cannot be established for most of these studies because exposure levels were not monitored or the subjects were exposed to several sulfur compounds. Animal data provide strong evidence that the respiratory tract is a sensitive target of hydrogen sulfide toxicity and can be used to establish concentration-response relationships. Damage to the nasal olfactory epithelium has been observed in rats exposed to hydrogen sulfide for acute or intermediate durations. Loss of olfactory neurons and basal cell hyperplasia were observed in rats exposed to 30 ppm and higher for 6 hours/day, 7 days/week for 10 or 13 weeks. The severity of the olfactory neuron loss was concentration-related. However, an inverse relationship between severity and concentration was observed for basal cell hyperplasia suggesting that as the concentration increased, the ability of the olfactory epithelium to regenerate decreased. Similar effects were observed in rats exposed to hydrogen sulfide once or repeatedly for 5 days; however, higher concentrations were needed to elicit a significant response. Intermediate-duration exposure (6 hours/day, 5 days/week for 13 weeks) resulted in inflammation of the squamous portion of the nasal mucosa in mice exposed to 80 ppm and loss of olfactory neurons in mice exposed to 30 ppm and higher.

**Neurological Effects.** A brief exposure to very high concentrations of hydrogen sulfide can result in unconsciousness in humans and animals followed by an apparent full recovery upon exposure termination (some human case reports note that the subjects recovered after administration of oxygen). Human data are not reliable for establishing the threshold for this effect because exposure levels were not quantified. In rats, the threshold for severe central nervous system depression is between 400 and 800 ppm; exposure to 400 ppm was associated with lethargy. As noted previously, persistent neurological effects have been reported in humans recovering from hydrogen-sulfide induced unconsciousness. These effects include headaches, poor concentration ability and attention span, impaired short-term memory, and impaired motor function.

Exposure to hydrogen sulfide can also result in neurobehavioral effects in humans and animals. Alterations in balance, reaction time, visual field, and verbal recall were observed in individuals exposed to high concentrations of hydrogen sulfide for an acute duration and in individuals exposed to lower levels of hydrogen sulfide for a chronic duration; actual exposure data were not reported, hydrogen sulfide levels were estimated based on symptoms. The severity of effects appeared to be related to the duration of exposure as well as the exposure concentration. No alterations in performance on tests of acuity or visual contrast sensitivity, cognitive tests, or sway tests were observed in young adults exposed to 5 ppm hydrogen sulfide for 2 hours; however, the subjects did report an increase in anxiety related to

## 2. RELEVANCE TO PUBLIC HEALTH

odor irritation. Ecological studies of communities living near industrial sources of hydrogen sulfide have found increases in the occurrence of a number of neurological symptoms including headaches, loss of balance, memory loss, and fatigue. Several animal studies provide suggestive evidence that hydrogen sulfide exposure results in a decrease in motor activity and task response rate; the lowest adverse effect level for altered neurobehavioral performance is the decreased spontaneous motor activity observed in rats receiving nose-only exposure to 80 ppm, 3 hours/day for 5 days. A rat study found that intermediate-duration exposure to hydrogen sulfide did not adversely affect memory; however, learning a new complex task was adversely affected at 125 ppm (4 hours/day, 5 days/week).

***Carbonyl Sulfide.*** The limited information on the toxicity of carbonyl sulfide is from several lethality studies in rats, acute toxicity studies in rats, cardiotoxicity studies in rabbits, several neurotoxicity studies in rats, and a male reproductive toxicity study in rats. No human data were located and it is assumed that the effects observed in the animal studies are relevant to humans. In the absence of studies examining a wide range of potential end points, there are insufficient data to identify the most sensitive end point(s) of carbonyl sulfide toxicity.

An 11-day exposure to 151 ppm carbonyl sulfide (6 hours/day, 5 days/week for 11 exposures) resulted in a slight increase in methemoglobin levels in rats; however, even at the highest concentrations tested (453 ppm), the magnitude of the increases was <2.5% and was not considered toxicologically relevant. In rabbits exposed to 54 ppm continuously for 7 weeks, no vascular or myocardial ultrastructural changes were observed and no morphological alterations in the coronary or pulmonary arteries, aorta, or lungs were observed following continuous exposure to 54 ppm for 7 weeks, although 3/18 animals died at this concentration. In a male reproductive toxicity study, a decrease in pregnancy rate was observed in unexposed female rats mated to males exposed to 182 ppm for approximately 11 weeks. When exposed males were allowed to recover for 10 weeks prior to mating with unexposed females, no reproductive effects were observed.

The most reliably reported effect of carbonyl sulfide is neurotoxicity. Acute- and intermediate-duration studies indicate a steep concentration-response relationship in rats. No overt signs of neurotoxicity, neurophysiological alterations, alterations in motor activity or grip strength, or histological alterations were observed following 2–12 weeks of exposure to  $\geq 300$  ppm. However, exposure to 400 ppm for 2–12 weeks resulted in hypotonia and slight gait abnormalities, decreases in motor activity and grip strength, alterations in brainstem auditory evoked potentials, and necrosis, microgliosis, and/or neuronal loss were observed in the parietal cortex, putamen, posterior colliculi, and anterior olivary nuclei. Ataxia

## 2. RELEVANCE TO PUBLIC HEALTH

was observed at 453 ppm for at least six exposures and morphological alterations consisting of necrosis of the frontoparietal cortex, putamen, retrosplenial cortex, thalamus, anterior olivary nucleus, and posterior colliculi were observed after 10 days of exposure to 500 ppm. The histological damage in the brain appears to occur within a couple of days of exposure initiation and does not appear to worsen with prolonged exposure (up to 12 weeks); at 600 ppm, histological alterations were observed following a single 6-hour exposure.

**2.3 MINIMAL RISK LEVELS (MRLs)**

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for hydrogen sulfide and carbonyl sulfide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

***Inhalation MRLs for Hydrogen Sulfide******Acute-Duration Inhalation MRL***

- An MRL of 0.07 ppm has been derived for acute-duration inhalation exposure to hydrogen sulfide.

A small number of controlled exposure studies have examined the acute toxicity of hydrogen sulfide in humans; most of these have focused on potential respiratory and metabolic effects. No significant

## 2. RELEVANCE TO PUBLIC HEALTH

alterations in lung function (forced lung vital capacity, forced expiratory volume, bronchial responsiveness to a histamine challenge, airway resistance, and specific airway conductance) were observed in asthmatics exposed to 2 ppm for 30 minutes (Jappinen et al. 1990). However, 2 of the 10 subjects had >30% changes in airway resistance and specific airway conductance, suggestive of bronchial obstruction. Three of the subjects also reported headaches. A series of studies conducted by Bhambhani and associates examined the potential of hydrogen sulfide to induce respiratory and metabolic effects in exercising adults. No significant alterations in lung function were observed in individuals exposed to 10 ppm for 15 minutes (Bhambhani et al. 1996a), but increases in blood lactate levels were observed in subjects exposed to 5 or 10 ppm (Bhambhani and Singh 1991; Bhambhani et al. 1997). The study authors noted that the increase in lactate levels suggested an increased dependence on anaerobic metabolism, which may have resulted from reduced oxygen availability due to detoxification of hydrogen sulfide by oxyhemoglobin or inhibition of cytochrome oxidase in exercising tissue (Bhambhani 1999). Fiedler et al. (2008) found no alterations in acuity or visual contrast sensitivity tests, cognitive tests, or postural sway in healthy young adults exposed to 5 ppm for 2 hours. A decline in verbal learning over the exposure period was also observed in subjects exposed to 0.05 or 0.5 ppm, relative to the 5 ppm group. The investigators suggested that this was probably due to fatigue or attention lapses during exposure; whether hydrogen sulfide contributed to this effect is not known. The subjects reported an increase in anxiety at 5 ppm, which was related to odor irritation rather than neurotoxicity. The subjects exposed to 5 ppm also reported an increase in lower and upper respiratory symptoms; however, the change was only 1–2 points on a 100-point scale and was not considered clinically significant.

Animal studies have reported a variety of respiratory effects following acute-duration exposure to hydrogen sulfide. Damage to the nasal olfactory epithelium was observed in rats exposed to 400 ppm for 4 hours (Lopez et al. 1988b), 200 ppm for 3 hours (Brenneman et al. 2002), or 80 ppm 3 hours/day for 5 days (Brenneman et al. 2002). Pulmonary edema has been observed in rats exposed to 83 or 375 ppm for 4 hours (Lopez et al. 1988a; Prior et al. 1990). Neurological effects included decreased spontaneous motor activity in rats exposed to 80 ppm, 3 hours/day for 5 days (Struve et al. 2001), impaired performance on a discriminated avoidance task in rats exposed to 200 ppm for 2 hours (Higuchi and Fukamachi 1977), lethargy in rats exposed to 400 ppm for 4 hours (Lopez et al. 1988b), and unconsciousness in rats exposed to 800 ppm for 20 minutes (Beck et al. 1979).

The Jappinen et al. (1990) study, which found suggestive evidence of bronchial obstruction among asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes, was selected as the basis of the MRL. The 2 ppm concentration was considered a minimally adverse effect level because the changes in airway

## 2. RELEVANCE TO PUBLIC HEALTH

resistance and specific airway conductance were only observed in 2 of the 10 subjects. The lowest-observed-adverse-effect level (LOAEL) from the Jappinen et al. (1990) study is supported by the LOAEL of 5 ppm for increased blood lactate levels observed in exercising subjects (Bhambhani et al. 1996b). The Jappinen et al. (1990) study was selected over the Bhambhani et al. (1996b) study because the Bhambhani studies involved mouth-only exposure so that the subjects could not smell the hydrogen sulfide. The MRL was calculated by dividing the unadjusted LOAEL by an uncertainty factor of 27 (3 for use of a minimal LOAEL, 3 for human variability, and 3 for database deficiencies). A partial uncertainty factor of 3 was used for human variability because the study was conducted in asthmatics who are likely to be a sensitive subpopulation. The uncertainty factor for database deficiencies was used to account for the short (30-minute) exposure duration of the Jappinen et al. (1990) study. Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

***Intermediate-Duration Inhalation MRL.***

- An MRL of 0.02 ppm has been derived for intermediate-duration inhalation exposure to hydrogen sulfide.

There are limited data on the toxicity of hydrogen sulfide in humans following intermediate-duration exposure. Acute- and chronic-duration studies suggest that the respiratory tract and nervous system are sensitive targets of hydrogen sulfide.

Intermediate-duration animal studies support the identification of the respiratory tract and nervous system as sensitive targets. Exposure of rats and mice to low hydrogen sulfide concentrations have resulted in histological damage to the upper respiratory tract. Brenneman et al. (2000) reported significant concentration-related increases in the incidence and severity of lesions to the nasal olfactory epithelium in rats exposed to hydrogen sulfide for 10 weeks. The effects consisted of olfactory neuron loss and basal cell hyperplasia in rats exposed to 30 or 80 ppm, 6 hours/day, 7 days/week for 10 weeks; no adverse effects were observed at 10 ppm. In contrast, earlier studies conducted by CIIT (1983b, 1983c) did not find significant alterations in the nasal turbinates of Sprague-Dawley or Fischer-344 (F-344) rats exposed to 80 ppm or less hydrogen sulfide, 6 hours/day, 5 days/week for 13 weeks. Inflammation of the squamous portion of the nasal mucosa was observed in mice exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks (CIIT 1983a); the no-observed-adverse-effect level (NOAEL) for this effect is 30 ppm. However, a re-examination of the histological specimens from this study (Dorman et al. 2004) revealed a statistically significant increase in the incidence of olfactory neuron loss in Sprague-Dawley rats, F-344 rats, and B6C3F<sub>1</sub> mice exposed to 30 or 80 ppm; no lesions were observed at

## 2. RELEVANCE TO PUBLIC HEALTH

10 ppm. In addition, increases in the incidence of bronchiolar epithelial hyperplasia and hypertrophy were observed in female Sprague-Dawley rats exposed to 30 or 80 ppm and male Sprague-Dawley and F-344 rats exposed to 80 ppm. The sensitivity of the olfactory epithelium has also been confirmed by acute-duration studies; degeneration of the olfactory epithelium was observed in rats exposed to 400 ppm hydrogen sulfide for 4 hours (Lopez et al. 1988b), rats exposed to 200 ppm for 3 hours (Brenneman et al. 2002), and rats exposed to 80 ppm, 3 hours/day for 5 days (Brenneman et al. 2002). Additionally, data collected using a computational fluid dynamics model of the rat nasal epithelium (Moulin et al. 2002) suggest that the olfactory epithelium is more sensitive than the nasal respiratory epithelium despite the higher hydrogen sulfide flux (a surrogate for dose) to the regions lined with respiratory epithelium compared to regions lined with olfactory epithelium. Within the areas of the nose lined with olfactory epithelium, a high correlation between predicted hydrogen sulfide flux and the incidence of olfactory lesions was found.

The neurotoxicity of hydrogen sulfide in mature animals following intermediate-duration exposure has been assessed in studies examining brain weight, neurological function (posture, gait, tone of facial muscles, and pupillary reflexes), and histopathology; neurobehavioral performance has not been adequately assessed in longer duration studies. A 5% decrease in absolute brain weight was observed in Sprague-Dawley rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 5 days/week for 13 weeks; no alterations were observed at 30 ppm (CIIT 1983c). No alterations in histopathology or neurological function were observed in these rats (CIIT 1983c) or in similarly exposed F-344 rats (CIIT 1983b) or B6C3F<sub>1</sub> mice (CIIT 1983a). Neurodevelopmental toxicity studies have found some alterations that are suggestive of neurotoxicity. The suggestive findings in the offspring of rats exposed for 7 hours/day on gestational day 5 through postnatal day 21 include alterations in the architecture and growth characteristics of Purkinje cell dendritic fields at 20 ppm (Hannah and Roth 1991), decreases in norepinephrine and increases in serotonin in the frontal cortex at 20 ppm (Skrajny et al. 1992), and decreases in brain amino acid levels at 75 ppm (Hannah et al. 1989, 1990). However, no alterations in neurobehavioral performance (assessed via motor activity, passive avoidance, acoustic startle, and functional observation battery), delays in development (pinnae detachment, surface righting, incisor eruption, negative geotaxis, and eyelid detachment), or neuropathology were observed in the offspring of rats exposed to 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 2 weeks prior to mating, during mating, on gestational days 5–19, and on postnatal days 5–18 (Dorman et al. 2000). These data suggest that exposures of 20–80 ppm may result in subclinical alterations in neurochemistry and neuroanatomy.

## 2. RELEVANCE TO PUBLIC HEALTH

The Brenneman et al. (2000) study was selected as the basis of the intermediate-duration inhalation MRL. In this study, groups of 12 male Sprague-Dawley rats were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide for 6 hours/day, 7 days/week for 10 weeks. Parameters used to assess toxicity were limited to extensive histopathological examination of the nasal cavity. Nasal lesions occurred only in the olfactory mucosa in rats exposed to 30 or 80 ppm and consisted of multifocal, bilaterally symmetrical olfactory neuron loss and basal cell hyperplasia affecting the lining of the dorsal medial meatus and the dorsal and medial regions of the ethmoid recess. No olfactory lesions were observed in the controls or rats exposed to 10 ppm.

The Brenneman et al. (2000) study was selected over the neurodevelopmental studies (Hannah and Roth 1991; Skrajny et al. 1992) that identified a slightly lower LOAEL (20 ppm, 7 hours/day, gestation day 5 to postnatal day 21) because the respiratory tract effects have been confirmed by other studies (Brenneman et al. 2002; Lopez et al. 1988b) and the adversity of the alterations in neurochemistry and neuroanatomy in the absence of neurological performance alterations is not known. As discussed by Ferguson (1996), prenatal exposure to ionizing radiation can result in misalignment of Purkinje cells in the cerebellum; clinical signs associated with these neuroanatomical alterations include hypoactivity, ataxia, tremors, and learning deficits. A direct comparison of the Purkinje cell alterations reported in the Hannah and Roth (1991) study and those resulting from ionizing radiation exposure cannot be made because the Hannah and Roth study involved examination of a single Purkinje cell rather than cerebellar sections. However, it may be reasonable to predict that the clinical manifestations of the Purkinje cell damage would be similar. The similarity of the LOAELs for nasal effects and neurodevelopmental effects suggest that an MRL derived for one would be protective of the other.

Because the incidence of olfactory neuron loss and basal cell hyperplasia went from 0 to 83–92% with no intermediate levels of response, the data were not considered suitable for benchmark dose analysis; thus, the MRL was derived using the NOAEL/LOAEL approach. A dosimetric model was used to estimate a concentration for humans that would be equivalent to the exposure concentration in rats; the model takes into account species differences in the surface area of the upper respiratory tract and inhalation rates. However, it does not take into consideration that a larger portion of the rat nasal cavity is lined with olfactory epithelium compared to humans (50% in rats compared to 10% in humans) and differences in air flow patterns. A computational fluid dynamics model (Moulin et al. 2002; Schroeter et al. 2006a, 2006b) of the rat nasal epithelium developed for hydrogen sulfide found strong correlations between the amount of hydrogen sulfide reaching the olfactory tissue and the severity of the lesions (Moulin et al. 2002) and between hydrogen sulfide flux (uptake by the olfactory tissue) and the lesion incidence

## 2. RELEVANCE TO PUBLIC HEALTH

(Schroeter et al. 2006a). Although Schroeter et al. (2006a) used the computational fluid dynamics model and the data from the Brennenman et al. (2000) rat study to predict a no-effect level in humans, there is some uncertainty in the extrapolation because the model is based on data from a single adult male and does not take into considerable interindividual variations. A subsequent study (Schroeter et al. 2010) in seven normal, healthy individuals (five adults and two children, aged 7 and 8 years) found that variations in nasal anatomy and olfactory airflow had little impact on hydrogen sulfide tissue flux in the olfactory region; the variation in tissue flux was <1.2. However, the study did not address potential variations in a wide range of childhood ages (including newborns and infants) or the sensitivity of hydrogen sulfide dosimetry to variation in pharmacokinetic parameters. Using the dosimetric model, the NOAEL of 10 ppm was adjusted for intermittent exposure (6 hours/day, 7 days/week) and multiplied by the ratio of rat to human ventilation rate to nasal cavity surface area (described in greater detail in Appendix A). The resultant NOAEL<sub>HEC</sub> of 0.46 ppm was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an MRL of 0.02 ppm.

***Chronic-Duration Inhalation MRL.*** Several human studies have examined the chronic toxicity of inhaled hydrogen sulfide (Ahlborg 1951; Deane et al. 1977; Hemminki and Niemi 1982; Jaakkola et al. 1990; Jappinen et al. 1990; Kangas et al. 1984; Schechter et al. 1989; Tenhunen et al. 1983). Most of these studies reported increases in the occurrence of subjective symptoms of respiratory irritation in workers or residents living near paper mills. Limitations, such as poor exposure characterization (including the lack of information on peak exposure levels) and co-exposure to other chemicals, limit the use of these studies for MRL derivation. No animal studies examined the chronic toxicity of hydrogen sulfide. Thus, a chronic-duration inhalation MRL was not derived.

***Oral MRLs for Hydrogen Sulfide.*** Information on the toxicity of hydrogen sulfide following oral exposure is limited to a dietary exposure study in pigs (Wetterau et al. 1964). The observed effects include a 23% decrease in body weight gain at 6.7 mg/kg/day in pigs exposed for 105 days and diarrheic digestive disturbances in pigs exposed to 15 mg/kg/day for a few days. Interpretation of this study is limited because very few details are reported, (e.g., no information on strain, methods used, number of animals studied, or statistics). This study was considered inadequate for MRL derivation.

***Inhalation MRLs for Carbonyl Sulfide.*** The inhalation toxicity database for carbonyl sulfide was considered inadequate for derivation of MRLs. A small number of studies have examined the toxicity of carbonyl sulfide in rats and rabbits following acute- or intermediate-duration exposure and have identified

## 2. RELEVANCE TO PUBLIC HEALTH

the nervous system and possibly the reproductive system as targets of toxicity. However, none of these studies adequately assessed other potential targets of toxicity. No morphological alterations were observed in the lungs, heart, or arteries of rabbits continuously exposed to 54 ppm carbonyl sulfide for 7 weeks; 3/18 animals died at this concentration (Kamstrup and Hugod 1979). Morphological effects in the brain and behavioral effects were observed in rats exposed to  $\geq 400$  ppm for 2–12 weeks (Herr et al. 2007; Monsanto 1985b; Morgan et al. 2004; Morrison et al. 2009; Sills et al. 2004); no effects were observed at 300 ppm. A decrease in pregnancy rates was observed in unexposed female rats mated with males exposed to 182 ppm carbonyl sulfide for 11 weeks (Monsanto 1987). Additional studies examining potential morphological alterations in major tissues and organs, reproductive toxicity in males and females, and possibly developmental toxicity are needed to identify critical targets of toxicity and to establish dose-response relationships.

***Oral MRLs for Carbonyl Sulfide.*** No oral MRLs were derived for carbonyl sulfide because no oral exposure studies in humans or animals were located.