DRAFT
TOXICOLOGICAL PROFILE FOR
HYDROGEN SULFIDE AND CARBONYL SULFIDE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

October 2014

DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Hydrogen Sulfide was released in 2006. This present edition supersedes any previously released draft or final profile. Additionally, carbonyl sulfide has been added to the updated hydrogen sulfide toxicological profile. Both hydrogen sulfide and carbonyl sulfide have been detected in emission tests of "Chinese drywall" samples.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30333

Physical Mailing Address:
4770 Buford Highway
Building 106, 3rd floor, MS F-57
Chamblee, Georgia 30341

Or

http://www.regulations.gov

Background Information

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i) (1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i) (3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i) (1) (B), to respond to requests for consultation under section 104(i) (4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Robin M. Ikeda, M.D., M.P.H.
Acting Assistant Administrator
Agency for Toxic Substances and Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials

incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Clinical Resources

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for hydrogen sulfide and carbonyl sulfide. The panel consisted of the following members:

1. Dr. Rui Wang, Office of VP Research, Lakehead University, Thunder Bay, Ontario, Canada;

2. Dr. Steven C. Lewis, Principal Scientist, Integrative Policy & Science, Inc., Adjunct Professor, Robert Wood Johnson Medical School, Washington, New Jersey; and

3. Dr. Alan Hall, Clinical Assistant Professor, Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver, Colorado.

These experts collectively have knowledge of hydrogen sulfide and carbonyl sulfide's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I) (13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT

1.1 PUBLIC HEALTH STATEMENT FOR HYDROGEN SULFIDE

Overview

We define a public health statement and show how it can help you learn about hydrogen sulfide.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by the Agency for Toxic Substances and Disease Registry's (ATSDR's) Division of Toxicology and Human Health Sciences (DTHHS). A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines hydrogen sulfide and carbonyl sulfide. This section of the public health statement summarizes the DTHHS's findings on hydrogen sulfide, describes the effects of exposure to it, and describes what you can do to limit that exposure.

Hydrogen sulfide at hazardous waste sites

The U.S. Environmental Protection Agency (U.S. EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites on the National Priorities List (NPL) and targets them for federal clean-up activities. U.S. EPA has found hydrogen sulfide in at least 35 of the 1,689 current or former NPL sites.

The total number of NPL sites evaluated for hydrogen sulfide is not known. However, the possibility remains that as more sites are evaluated, the number of sites at which hydrogen sulfide is found may increase. This information is important; these future sites may be sources of exposure, and exposure to hydrogen sulfide may be harmful.

A hydrogen sulfide release may be harmful

When a contaminant is released from a large area such as an industrial plant or from a container such as a drum or bottle, it enters the environment. However, such a release doesn't always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you're exposed to hydrogen sulfide, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you are exposed. Harm might also depend on whether you've been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

A Closer Look at Hydrogen Sulfide

Overview

This section describes hydrogen sulfide in detail and how you can be exposed to it.

What is hydrogen sulfide

Hydrogen sulfide (H_2S) is a flammable, colorless gas that smells like rotten eggs. People usually can smell hydrogen sulfide at low concentrations in air, ranging from 0.0005 to 0.3 parts per million (ppm) (0.0005–0.3 parts of hydrogen sulfide in 1 million parts of air). At high concentrations, a person might lose their ability to smell it. This is important because a person might falsely think that hydrogen sulfide is no longer present; this may increase their exposure risk to air levels that may cause serious health effects.

Hydrogen sulfide occurs both naturally and from human-made processes. It is in the gases from volcanoes, sulfur springs, undersea vents, swamps, and stagnant bodies of water and in crude petroleum and natural gas. Hydrogen sulfide also is associated with municipal sewers and sewage treatment plants, swine containment and manure-handling operations, and pulp and paper operations. Industrial sources of hydrogen sulfide include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, food processing plants, and tanneries. Bacteria found in your mouth and gastrointestinal tract produce hydrogen sulfide during the digestion of food containing vegetable or animal proteins.

How is hydrogen sulfide used

Hydrogen sulfide is used primarily in the production of sulfur and sulfuric acid. It can also be used to make other chemicals such as sodium sulfide and sodium hydrosulfide, which are used to make a variety of products including dyes, pesticides, and pharmaceuticals. Hydrogen sulfide is utilized in the purification of nickel and manganese as well as hydrochloric and sulfuric acids. It is used in metallurgy, the nuclear industry, and in laboratory experiments. It is also an agricultural disinfectant.

Where is hydrogen sulfide found

Hydrogen sulfide can be released into the air, water, and soil at places where it is produced or used.

Possible Sources	Outcome
Air: Most of the hydrogen sulfide released to air comes from natural sources such as swamps, bogs, and volcanoes. Hydrogen sulfide can also be released from industrial sources such as petroleum refineries, natural gas plants, kraft paper mills, manure treatment facilities, waste water treatment facilities, and tanneries. Hydrogen sulfide air concentrations from natural sources range between 0.00011 and 0.00033 ppm. In urban areas, the air concentrations are generally less than 0.001 ppm.	Hydrogen sulfide remains in the atmosphere for approximately 1–42 days, depending on the season. It can change into sulfur dioxide and sulfates in the air.
Water: Hydrogen sulfide might be released to water in liquid waste of an industrial facility or as the result of a natural event. It can be naturally present in well water.	Hydrogen sulfide concentrations in surface water are usually very low because it readily evaporates from water. It can also be present in groundwater.
Soil: Hydrogen sulfide can enter soil through atmospheric deposition or from spills.	In soil, hydrogen sulfide is consumed by bacteria, which change it to sulfur.

How Hydrogen Sulfide Can Affect Your Health

Overview

This section looks at how hydrogen sulfide enters your body and potential hydrogen sulfide health effects found in human and animal studies.

How hydrogen sulfide enters your body

Hydrogen sulfide enters your body primarily through the air you breathe. Much smaller amounts can enter your body through the skin. Hydrogen sulfide is a gas, so you would not likely be exposed to it by ingestion. When you breathe air containing hydrogen sulfide or when hydrogen sulfide comes into contact with skin, it is absorbed into the blood stream and distributed throughout the body.

How hydrogen sulfide leaves your body

In the body, hydrogen sulfide is primarily converted to sulfate and is excreted in the urine. Hydrogen sulfide is rapidly removed from the body.

Hydrogen sulfide health effects

The health effects of hydrogen sulfide depend on several factors such as how much hydrogen sulfide you are exposed to and the length of that exposure. Studies in workers, communities living near industrial sources of hydrogen sulfide, and volunteers suggest that the respiratory tract and nervous system are the most sensitive targets of hydrogen sulfide toxicity. No health effects have been found in humans exposed to typical environmental concentrations of hydrogen sulfide (0.00011–0.00033 parts per million [ppm]).

Respiratory effects

Exposure to low concentrations of hydrogen sulfide may cause irritation to the eyes, nose, or throat. It may also cause difficulty in breathing for some asthmatics.

Respiratory distress or arrest has been found in people exposed to very high concentrations of hydrogen sulfide.

Nervous system effects

Exposure to low concentrations of hydrogen sulfide may cause headaches, poor memory, tiredness, and balance problems.

Brief exposures to high concentrations of hydrogen sulfide (greater than 500 ppm) can cause a loss of consciousness. In most cases, the person appears to regain consciousness without any other effects. However, in some individuals, there may be permanent or long-term effects such as headaches, poor attention span, poor memory, and poor motor function.

Hydrogen sulfide and cancer

Hydrogen sulfide has not been shown to cause cancer in humans, and its possible ability to cause cancer in animals has not been studied thoroughly.

DHHS and the International Agency for Research on Cancer (IARC) have not classified hydrogen sulfide as to its carcinogenicity.

EPA has determined that data for hydrogen sulfide are inadequate for carcinogenic assessment.

See Chapters 2 and 3 for more information on the health effects from exposure to hydrogen sulfide.

Children and Hydrogen Sulfide

Overview

This section discusses potential health effects of hydrogen sulfide exposure in humans from when they're first conceived to 18 years of age, and how you might protect against such effects.

Exposure effects for children

There is very little information on possible health problems in children who have been exposed to hydrogen sulfide. Exposed children probably will experience effects similar to those experienced by exposed adults. Whether children are more sensitive to hydrogen sulfide exposure than adults is not known.

What about birth defects

It is not known whether exposure to hydrogen sulfide causes birth defects in humans. The results of studies in animals suggest that exposure to low concentrations of hydrogen sulfide during pregnancy does not cause birth defects.

How Can Families Reduce the Risk of Exposure to Hydrogen Sulfide?

If your doctor finds that you have been exposed to significant amounts of hydrogen sulfide, ask whether your children or unborn baby might also be exposed. Your doctor might need to ask your state health department to investigate.

Air

Hydrogen sulfide is part of the natural environment; the general population will have some exposure to hydrogen sulfide. Families can be exposed to more hydrogen sulfide than the general population if they live near natural or industrial sources of hydrogen sulfide, such as hot springs, manure holding tanks, or pulp and paper mills. However, their exposure levels are unlikely to approach those that sicken people exposed at work.

Reducing your exposure to hydrogen sulfide

Families can reduce their exposure to hydrogen sulfide by avoiding areas that are sources of hydrogen sulfide. For example, individuals of families that live on farms can avoid manure storage areas where high concentrations of hydrogen sulfide may be found.

Medical Tests to Determine Hydrogen Sulfide Exposure

Overview

We identify medical tests that can detect whether hydrogen sulfide is in your body.

Hydrogen sulfide can be measured in blood and urine

Hydrogen sulfide and its breakdown products such as thiosulfate can be measured in blood and urine. However, the detection of hydrogen sulfide or its metabolites cannot predict the kind of health effects that might develop from that exposure. Because hydrogen sulfide and its metabolites leave the body fairly rapidly, the tests need to be conducted soon after exposure.

For more information on the different substances formed by hydrogen sulfide breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

Toxic substance recommendations

The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Not-to-exceed levels

Regulations and recommendations can be expressed as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (for example, an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Some regulations and recommendations for hydrogen sulfide exposure in workers include:

Federal Organization	Regulation or Recommendation
Occupational Safety and Health Administration (OSHA)	OSHA set an acceptable ceiling limit of 20 ppm for hydrogen sulfide in workplace air; the ceiling limit is a 15-minute time-weighted average that cannot be exceeded at any time during the working day.
National Institute for Occupational Safety and Health (NIOSH)	NIOSH recommends a 10-minute ceiling level of 10 ppm for workers. NIOSH also determined that 100 ppm is immediately dangerous to life or health to workers.

1.2. PUBLIC HEALTH STATEMENT FOR CARBONYL SULFIDE

Overview

We define a public health statement and show how it can help you learn about carbonyl sulfide.

Introduction

A public health statement summarizes information about a hazardous substance. The information is taken from a toxicological profile developed by the Agency for Toxic Substances and Disease Registry's (ATSDR's) Division of Toxicology and Human Health Sciences (DTHHS). A toxicological profile is a thorough review of a hazardous substance.

This toxicological profile examines hydrogen sulfide and carbonyl sulfide. This section of the public health statement summarizes the DTHHS's findings on carbonyl sulfide describes the effects of exposure to it, and describes what you can do to limit that exposure.

Carbonyl sulfide at hazardous waste sites

The U.S. Environmental Protection Agency (U.S. EPA) identifies the most serious hazardous waste sites in the nation. U.S. EPA then includes these sites on the National Priorities List (NPL) and targets them for federal clean-up activities. U.S. EPA has found carbonyl sulfide in at least 3 of the 1,689 current or former NPL sites.

The total number of NPL sites evaluated for carbonyl sulfide is not known. However, the possibility remains that as more sites are evaluated, the number of sites at which carbonyl sulfide is found may increase. This information is important; these future sites may be sources of exposure, and exposure to carbonyl sulfide may be harmful.

A carbonyl sulfide release may be harmful

When a contaminant is released from a large area such as an industrial plant or from a container such as a drum or bottle, it enters the environment. However, such a release doesn't always lead to exposure. You can only be exposed to a contaminant when you come in contact with it. That contact—and therefore that exposure—can occur when you breathe, eat, or drink the contaminant, or when it touches your skin.

Even if you're exposed to carbonyl sulfide, you might not be harmed. Whether you are harmed will depend on such factors as the dose (how much), the duration (how long), and how you are exposed. Harm might also depend on whether you've been exposed to any other chemicals, as well as your age, sex, diet, family traits, lifestyle, and state of health.

A Closer Look at Carbonyl Sulfide

Overview

This section describes carbonyl sulfide in detail and how you can be exposed to it.

What is carbonyl sulfide

Carbonyl sulfide (COS) is a colorless gas that smells like rotten eggs; it does not have an odor when it is free from impurities. Carbonyl sulfide can also be called carbon oxide sulfide and carbon oxysulfide.

At concentrations of 135 micrograms per cubic meter ($\mu g/m^3$) (0.055 ppm), people may be able to smell carbonyl sulfide in air.

Carbonyl sulfide is present in both natural and human-made sources. It can be found in volcanic gases, crude petroleum oil, sulfurous waters, marshes, and soils. It is in the emissions from diesel engines, natural gas and refinery emissions, and tobacco smoke.

How is carbonyl sulfide used

Carbonyl sulfide does not have many commercial uses, as it is primarily used in small-scale chemical syntheses. It is an intermediate in the manufacture of certain herbicides. It may also be used in the agricultural industry as a grain fumigant.

Where is carbonyl sulfide found

Carbonyl sulfide can be released into the air, water, and soil at places where it is produced or used.

Possible Sources	Outcome
Air: Carbonyl sulfide is released to air from natural sources such as soils, wetlands, volcanoes, and oceans. It is also released during chemical processing, natural gas and oil recovery, combustion of coal, biomass, burning, and others. The average carbonyl sulfide level in outdoor air is 0.0018 ppm.	Carbonyl sulfide can remain in the atmosphere for 2–10 years.
Water: Carbonyl sulfide might enter water from atmospheric deposition.	Carbonyl sulfide reacts with water to form carbon dioxide and hydrogen sulfide. It is expected to rapidly volatilize to air.
Soil: Carbonyl sulfide might enter soil from atmospheric deposition.	Carbonyl sulfide does not bind to soil. It may move through the soil and enter groundwater.

How Carbonyl Sulfide Can Affect Your Health

Overview

This section looks at how carbonyl sulfide enters your body and potential carbonyl sulfide health effects found in human and animal studies.

How carbonyl sulfide enters your body	We know that carbonyl sulfide can enter your body from the air because health effects have been observed in studies with animals. We do not know how much or how fast it can enter your body.
How carbonyl sulfide leaves your body	We do not know how carbonyl sulfide is broken down in the body or how it leaves the body.
Carbonyl sulfide health effects	We have very little information on the health effects of carbonyl sulfide. Studies in animals show that nervous system effects can occur after short- or long-term exposure. The health effects of carbonyl sulfide appear to depend on several factors such as how much you are exposed to and the length of that exposure.
Nervous system effects	Animal studies show that exposure to high levels of carbonyl sulfide in the air can damage the areas of the brain that control movement and process sound information.
Carbonyl sulfide and cancer	No human or animal studies have examined whether carbonyl sulfide exposure can cause cancer. DHHS, the International Agency for Research on Cancer (IARC), and EPA have not classified carbonyl sulfide as to its carcinogenicity.

See Chapters 2 and 3 for more information on the health effects from exposure to carbonyl sulfide.

Children and Carbonyl Sulfide

Overview

This section discusses potential health effects of carbonyl sulfide exposure in humans from when they're first conceived to 18 years of age and how you might protect against such effects.

Exposure effects for children	There is no information on possible health problems in children who have been exposed to carbonyl sulfide. Exposed children probably will experience effects similar to those experienced by exposed adults. Whether children are more sensitive to carbonyl sulfide exposure than adults is not known.

What about birth defects

It is not known if exposure to carbonyl sulfide causes birth defects in humans. No studies looked for birth defects in animals.

How Can Families Reduce the Risk of Exposure to Carbonyl Sulfide?

If your doctor finds that you have been exposed to significant amounts of carbonyl sulfide, ask whether your children or unborn baby might also be exposed. Your doctor might need to ask your state health department to investigate.

Air

Carbonyl sulfide is part of the natural environment; the general population will have some exposure to carbonyl sulfide. Families can be exposed to more carbonyl sulfide than the general population if they live near natural or industrial sources of carbonyl sulfide, such as wetlands, volcanos, or coal combustion. However, their exposure levels are unlikely to approach those that sicken people exposed at work.

Reducing your exposure to carbonyl sulfide

Families can reduce their exposure to carbonyl sulfide by avoiding areas that are sources of carbonyl sulfide.

Medical Tests to Determine Carbonyl Sulfide Exposure

Overview

How carbonyl sulfide is broken down in the body and how it is removed from the body is not known. Thus, no medical tests have been identified that can determine carbonyl sulfide exposure.

Federal Government Recommendations to Protect Human Health

Overview

One way the federal government promotes public health is by regulating toxic substances or recommending ways to handle or to avoid toxic substances.

The federal government regulates toxic substances

Regulations are enforceable by law. The U.S. EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that have adopted toxic substances regulations.

Toxic substance recommendations

The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) have made recommendations about toxic substances. Unlike enforceable regulations, these recommendations are advisory only.

Not-to-exceed levels

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Some regulations and recommendations for carbonyl sulfide exposure in workers include:

Federal Organization	Regulation or Recommendation
Occupational Safety and Health Administration (OSHA)	OSHA has not established regulations for workers exposed to carbonyl sulfide.
National Institute for Occupational Safety and Health (NIOSH)	NIOSH has not established guidelines for workers exposed to carbonyl sulfide

Additional Information

Overview

Where to find more information about hydrogen sulfide and carbonyl sulfide:

Who to contact

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

Additional information from ATSDR

ATSDR can provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

Where to obtain toxicological profile copies

Toxicological profiles are also available online at www.atsdr.cdc.gov. For more information:

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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_2S) is a poisonous, 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_4^{2-}). 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 0.11 and 0.33 ppb. Concentrations of hydrogen sulfide in urban areas are generally <1 ppb. Much higher levels (often exceeding 90 ppb) 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 between 1 and 100 ppb 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. In these experiments, between 40 and 90% of normal individuals produced hydrogen sulfide; mean values over a 4-year period were between 1 and 4 ppm.

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. As reviewed, 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 $GABA_B$ 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 ≥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.

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 the 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,

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, punctuate 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 $\mu g/m^3$), medium (10–30 $\mu g/m^3$), or high (>30 $\mu g/m^3$) 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

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.

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

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. 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 recovery 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 ≥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 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 made 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 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 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$_1$ mice exposed to 30 or 80 ppm; no lesions were observed at 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 $B6C3F_1$ 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 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.

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 (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. 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 $NOAEL_{HEC}$ 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 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 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 ≥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.

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 and carbonyl 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

Hydrogen Sulfide. 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; Christia-Lotter et al. 2007; Knight and Presnell 2005; Yalamanachili and Smith 2008), animal processing plants (Breysse 1961), waste dumps (Allyn 1931), sludge plants (NIOSH 1985a), tanks and cesspools (Ago et al. 2008; 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; Policastro and Otten 2007). Some cases were suicides that involved mixing household chemicals such as hydrochloric acid and lime sulfur to generate hydrogen sulfide gas (Bott and Dodd 2013; Maebashi et al. 2011; Reedy et al. 2011). 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, 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) when 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 lost consciousness within a few minutes of entering a partially drained underground liquid manure storage tank and died before reaching the hospital. An autopsy showed that two of the men had massive liquid manure pulmonary aspiration, while the third man 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). In another report, 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). In another case, 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 along with 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 Māori (indigenous people of New Zealand) than in the rest of New Zealand, and because Māori disease and mortality rates are relatively high compared with those of the non-Māori population, further analysis was carried out with an

adjustment for ethnicity. When these data were stratified by sex and ethnicity, Māoris females 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 numerous issues with regard to ecologic studies; primarily confounding exposure to other agents (e.g., smoking) and 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 causing 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). However, 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). A third study reported that all six mice exposed to 722 ppm hydrogen sulfide for 50 minutes died; exposure of six mice to 1,872 ppm hydrogen sulfide resulted in death 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).

Carbonyl Sulfide. Two studies in male and female rats have calculated LC_{50} values of 1,082 and 1,111 ppm for a 4-hour exposure to carbonyl sulfide (DuPont 1981; Monsanto 1985a). Clinical signs observed at the higher concentrations (≥1,096 ppm) included convulsions, hypoactivity, and breathing difficulties (Monsanto 1985a). The mortality concentration-response curve was steep, with 40% of the animals dying at 1,090 ppm, 50% at 1,160 ppm, and 100% at ≥1,210 ppm (DuPont 1981).

Repeated exposures to lower concentrations also resulted in mortality or morbidity. Rats exposed to 500 ppm 6 hours/day for 4 days or 600 ppm for 2 days were sacrificed in moribund condition (Morgan et al. 2004); however, exposure to 400 ppm (6 hours/day, 5 days/week) for as long as 12 weeks did not result in mortality or extreme morbidity (Herr et al. 2007; Morgan et al. 2004; Sills et al. 2004). Approximately 20–40% mortality was observed in rabbits continuously exposed to 54 ppm for 5 days (Hugod 1981; Hugod and Astrup 1980; Kamstrup and Hugod 1979).

All reliable LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1 for hydrogen sulfide and Table 3-2 and Figure 3-2 for carbonyl sulfide.

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.

Hydrogen Sulfide. A variety of respiratory effects (including symptoms of respiratory irritation, altered lung function, and respiratory distress) have been observed in workers accidentally exposed to high concentrations of hydrogen sulfide, experimental subjects acutely exposed to low levels of hydrogen sulfide, chronically exposed workers, and residents living near pulp mill production facilities, hog feeding operations, or areas with high geothermal activity. It should be noted that with the exception of the

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	2x30 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	2 hr	Resp	5			Fiedler et al. 2008	
17	Human	30 min	Resp		2[b] (increased airway resistance and decreased specific airway conductance in 2/10 asthmatics)		Jappinen et al. 1990	
18	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
19	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	
20	Rat (Fischer- 344)	4 hr	Resp		194 M (increase in protein and lactate dehydrogenase in lavage fluid; focal areas of perivascular edema; proteinaceous material in the alveoli)		Green et al. 1991	
21	Rat (Wistar)	1 hr	Resp		100 M (increased respiration rate)		Higuchi and Fukamachi 1977	
			Cardio		100 M (increased blood pressure, heart rate)			
22	Rat (Fischer- 344)	4 hr	Resp	10 M	50 M (15% reduction in lung cytochrome c oxidase activity)		Khan et al. 1990	
23	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
24	Rat (Wistar)	20-60 min	Resp		75 M (slight congestion)		Kohno et al. 1991	
			Cardio			75 M (cardiac arrhythmia; decreased heart rate)		
25	Rat (Fischer- 344)	4 hr	Resp		10 M (increased cellularity in nasal lavage fluid)		Lopez et al. 1987	
26	Rat (Fischer- 344)	4 hr	Resp		83 M (mild perivascular edema)		Lopez et al. 1988a	
27	Rat (Fischer- 344)	4 hr	Resp			400 M (severe inflammation and necrosis of respiratory and olfactory epithelium)	Lopez et al. 1988b	
28	Rat (Fischer- 344)	4 hr	Ocular	200 M	400 M (epiphora)		Lopez et al. 1988b	
29	Rat (Fischer- 344)	4 hr	Resp			375 M (moderate to massive pulmonary edema)	Prior et al. 1990	
30	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
31	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								
32	Rat (Fischer- 344)	4 hr		50 M	200 M (decreased respiratory rate of pulmonary alveolar macrophages stimulated with zymosan)		Khan et al. 1991	
Neurological								
33	Human	2 hr		5			Fiedler et al. 2008	
34	Human	30 min			2 (headache in 3/10 asthmatics)		Jappinen et al. 1990	
35	Rat (Wistar)	20 min				800 M (unconsciousness)	Beck et al. 1979	
36	Rat (Wistar)	2 hr		100 M	200 M (decreased response rate in conditioned avoidance task)		Higuchi and Fukamachi 1977	
37	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
38	Rat (CD)	3 hr/d 5 d		30 M	80 M (decreased spontaneous motor activity)		Struve et al. 2001	
39	Gn Pig (NS)	11 d 1 hr/d			20 M (decreased cerebral hemisphere and brain stem total lipids and phospholipids)		Haider et al. 1980	
40	Rabbit (mixed breeds)	1.5 hr				72 (unconsciousness)	Kosmider et al. 1967	
INTERMEDIATE EXPOSURE								
Systemic								
41	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
42	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
43	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	30.5 F	80 F (10% decrease in body weight)			
44	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	
45	Rat (Sprague-Dawley)	Gd 1- 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
46	Rat (Sprague-Dawley)	Gd 6-20 6 hr/d	Bd Wt	100 F	150 F (pregnant rats lost weight)		Saillenfait et al. 1989	
47	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	10	80 (inflammation of nasal mucosa)		CIIT 1983a	
					30 (olfactory neuron loss in the nasal olfactory epithelium)			
			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
48	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								
49	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		80			CIIT 1983b	
50	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c	
51	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		80			CIIT 1983a	
Neurological								
52	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		80			CIIT 1983b	
53	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		30.5 M	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
54	Rat (Sprague-Dawley)	25 wk 5 d/wk		50 M			Gagnaire et al. 1986	
55	Rat (Sprague-Dawley)	4 hr/d 5 d/wk 5-11 wk			125 M (impaired learning of new tasks on a radial arm maze)		Partlo et al. 2001	
56	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		80			CIIT 1983a	
Reproductive								
57	Rat (Fischer- 344)	90 d 5 d/wk 6 hr/d		80			CIIT 1983b	
58	Rat (Sprague-Dawley)	90 d 5 d/wk 6 hr/d		80			CIIT 1983c	
59	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000	
60	Mouse (B6C3F1)	90 d 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								
61	Rat (Sprague-Dawley)	6 hr/d 7 d/wk 60-70 d		80			Dorman et al. 2000	
62	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	
63	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	
64	Rat (Sprague-Dawley)	Gd 1- Ppd 21 7 hr/d		75 F			Hayden et al. 1990a	
65	Rat (Sprague-Dawley)	Gd 1- Ppd 21 7 hr/d		75 F			Hayden et al. 1990b	
66	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
67	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.

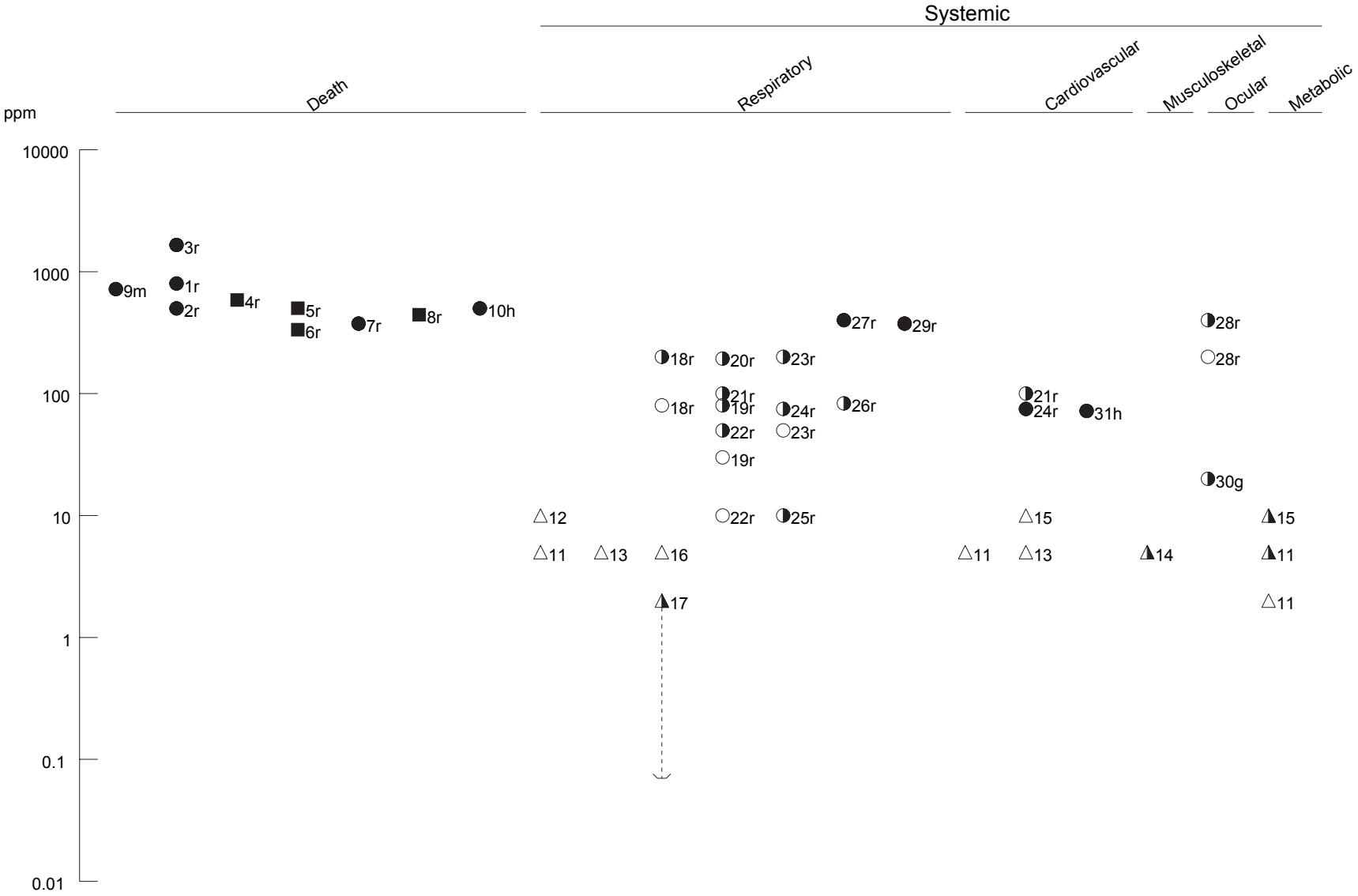
b Used to derive an acute-duration Minimal Risk Level (MRL) of 0.07 ppm; concentration divided by an uncertainty factor of 27 (3 for use of a minimal LOAEL, 3 for human variability, and 3 for database deficiencies).

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 (RDGR) for extrathoracic effects to calculate a human equivalent concentration (HEC). The NOAELHEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Metab = metabolism; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Ppd = post-parturition day; ppm = parts per million; Resp = respiratory; wk = week(s)

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

Acute (≤14 days)



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

◆ 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)*

Acute (≤14 days)

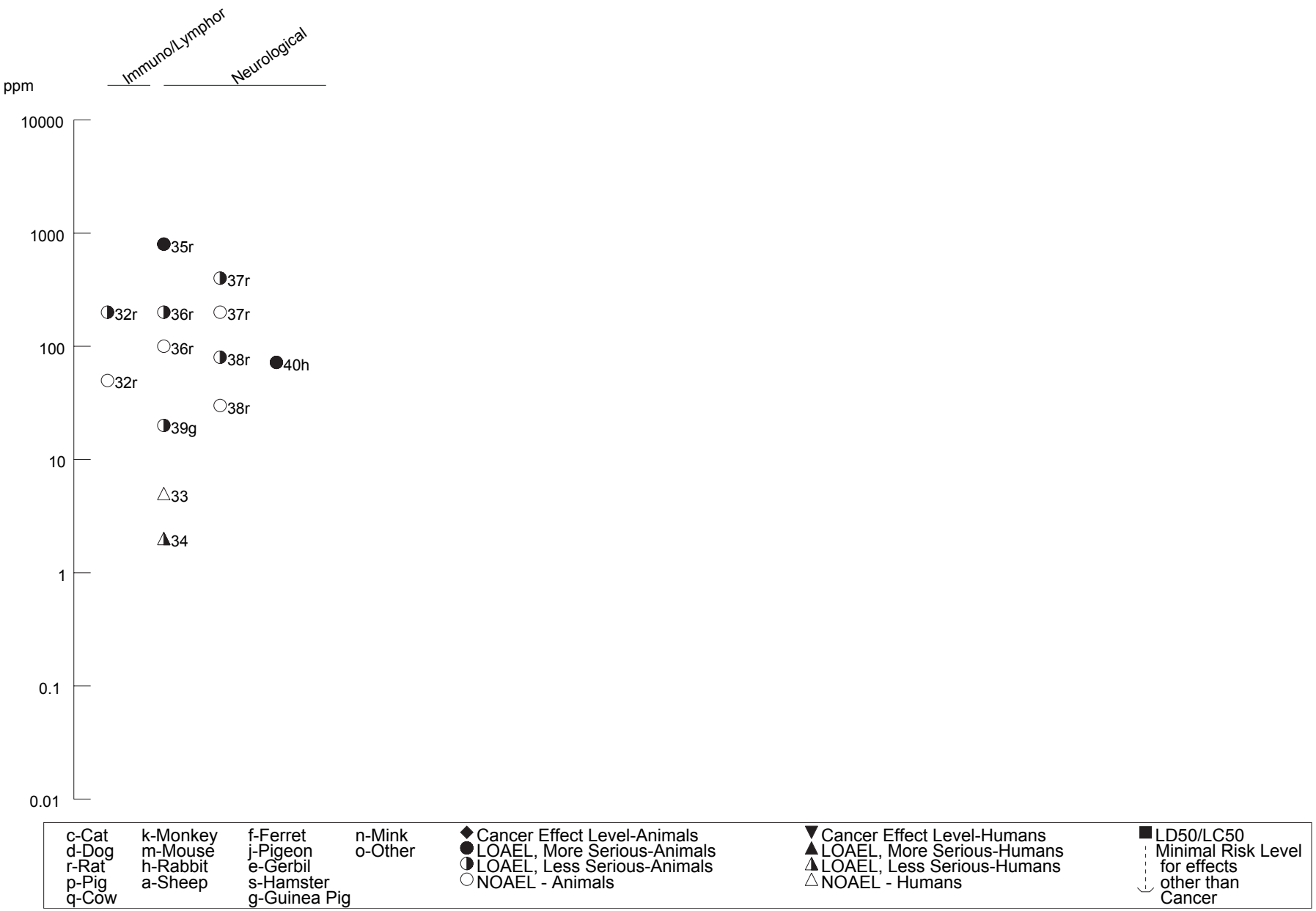


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(Continued)*

Intermediate (15-364 days)

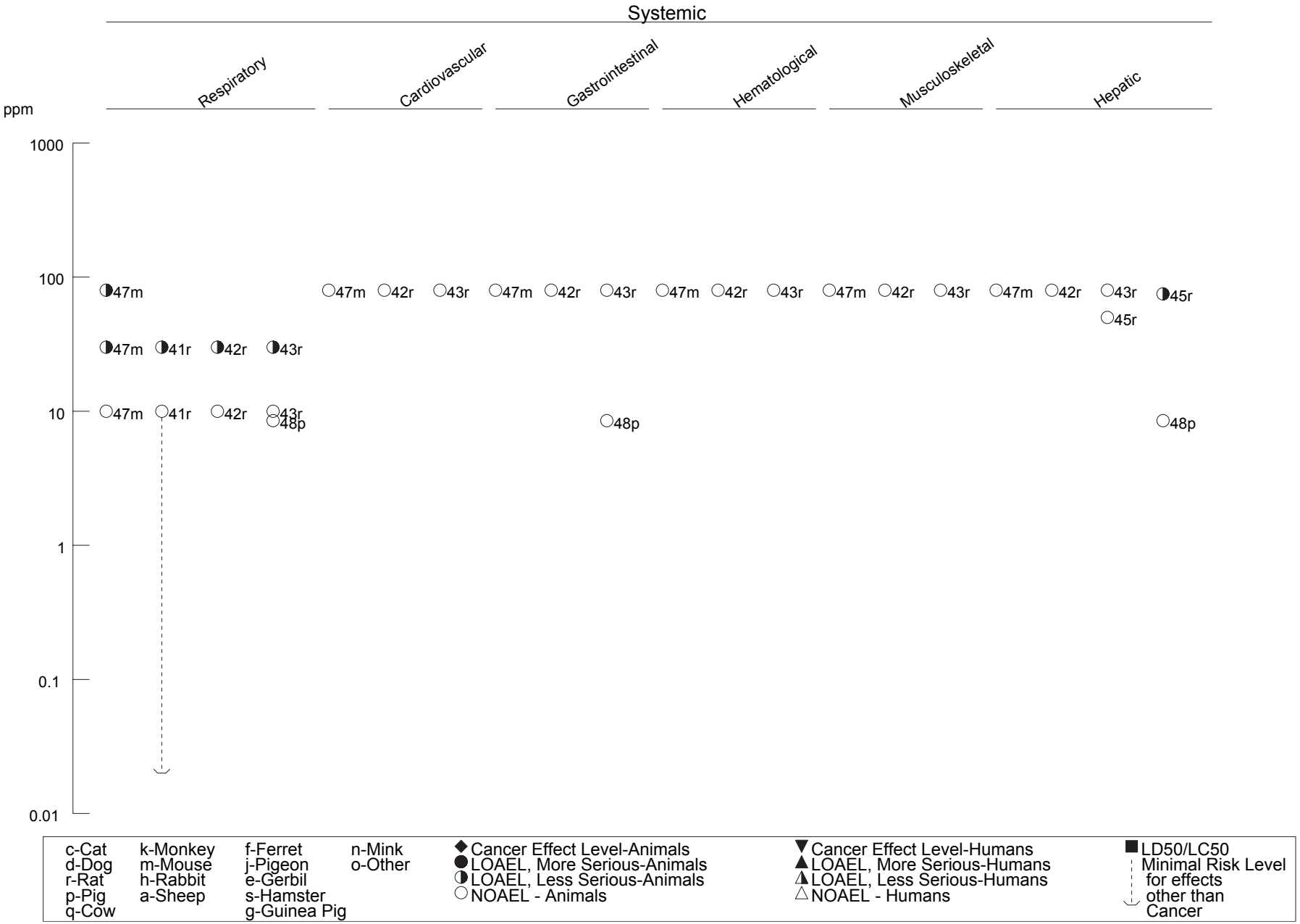


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(Continued)*

Intermediate (15-364 days)

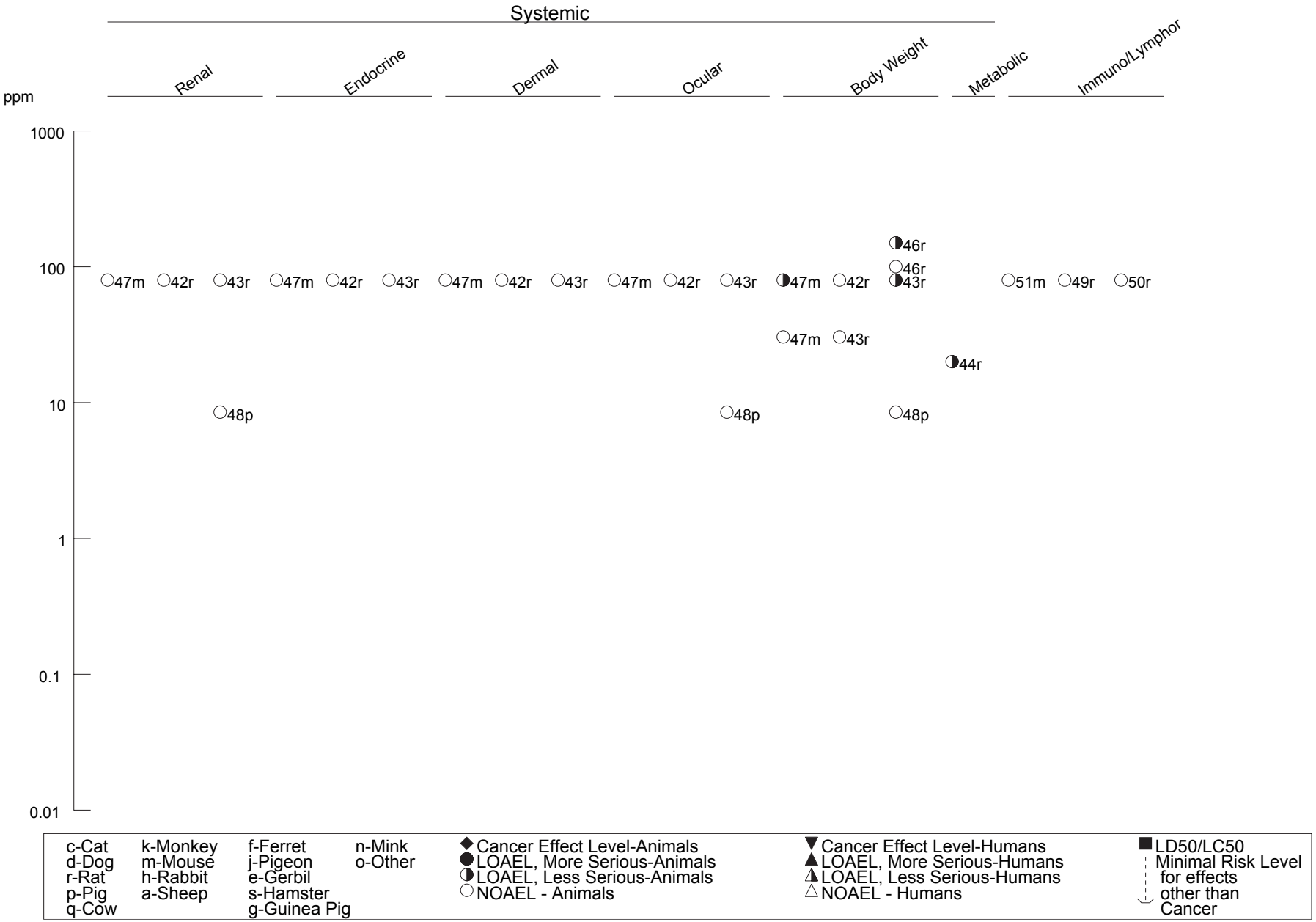
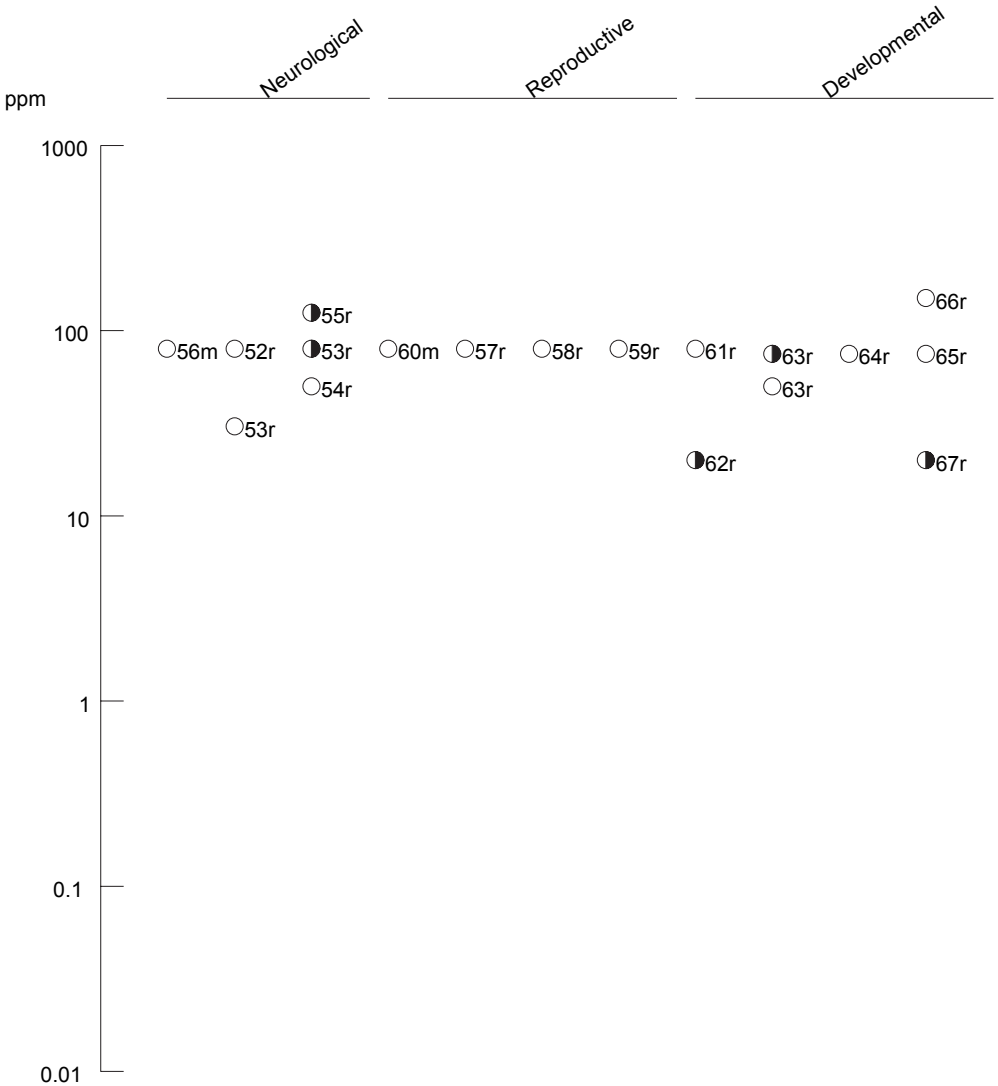


Figure 3-1 Levels of Significant Exposure to Hydrogen Sulfide - Inhalation *(Continued)*

Intermediate (15-364 days)



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

◆ 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

experimental studies, there was concominant exposure to a number of other compounds including ammonia, methyl mercaptan, methyl sulfides, sulfur dioxide, and particulate matter. 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). Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for <25 minutes (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).

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 $\mu g/m^3$ with 35% of the measurements >70 $\mu g/m^3$ and 10% of the measurements >400 $\mu g/m^3$. 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; however, the incidences of other diseases of the upper respiratory tract category 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.

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. Another study found a weak association between the 3-day moving average hydrogen sulfide atmospheric levels in Reykjavik Iceland and the number of individuals who were dispensed drugs for the treatment of asthma 3–5 days after the increased pollution; the excess risk was 2.0% (95% confidence interval [CI] of 0.4–3.6) (Carlsen et al. 2012). The study also found a weak association for PM_{10} levels.

An increase in symptoms of upper and lower respiratory irritation was observed in healthy, young adults exposed to 5 ppm hydrogen sulfide for 2 hours; however, the change was only 1– 2 points on a 100-point scale and was not considered clinically significant (Fiedler et al. 2008).

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, was reported by several investigators: Jaakkola et al. (1990), Haahtela et al. (1992), Marttila et al. (1994a, 1994b, 1995), and Partti-Pellinen et al. (1996). 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 total reduced sulfur (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.

In the Jaakkola et al. (1990) study, the responses of populations from three communities (a non-polluted 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 μg/m^3; 2.9 and 40 ppb) than in the moderately polluted one (2 and 22 μg/m^3; 1.4 and 16 ppb). Particulate measurements made concurrently, and sulfur dioxide measurements made subsequently, also showed higher levels in the severely polluted community. A cross-sectional, self-administered questionnaire was used to gather data on the occurrence (i.e., often or constantly) of a variety of respiratory symptoms and effects during two time periods (the past 4 weeks and the previous 12 months). The occurrences of nasal symptoms and cough were found to be significantly greater in the subjects living in the two polluted communities when compared to those in the nonpolluted community. Breathlessness/wheezing was also increased, although not to the level of statistical 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 in the Jaakkola et al. (1990) study and showed increased risks both for the 4-week and the 12-month intervals, although none of these risks reached statistical significance. Haahtela et al. (1992) reported a significant increase in the number of residents reporting breathlessness (35%) during a period of unusually high hydrogen sulfide levels. The maximum concentration was 135 μg/^{3} (0.096 ppm) with 24-hour average concentrations on 2 days of 35 and 43 μg/m^3 (0.025 and 0.031 ppm). The number of

residents reporting breathlessness was 2% 4 months later when the concentrations were lower (levels ranged from 0.1 to 3.5 μg/m^3 [0.00007–0.0025 ppm] during a 4-hour period).

Marttila et al. (1995) also examined the relationship between daily exposure to malodorous sulfur compounds (measured TRS) from pulp production and reporting of symptoms in a small population living in the vicinity of a pulp mill. During the study period, daily mean TRS concentrations varied from 0 to 82 μg/m^3, and monthly mean concentrations varied from 3 to 19 μg/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 μg/m^3, medium exposure 10–30 μg/m^3, and high exposure >30 μg/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 μg/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, this conclusion is 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 impact the interpretation of these findings.

A significant increase in respiratory symptoms (OR=11.92; 95% CI=4.37–12.42) was reported by residents living in two communities (Odessa, Texas and Puna, Hawaii) with chronic low levels of industrial sources of hydrogen sulfide, as compared to residents living in two comparable communities without known sources of hydrogen sulfide pollution (Legator et al. 2001). The most commonly reported respiratory symptoms were wheezing (25–30%), shortness of breath (40–45%), and persistent cough (10%); each of these effects had an incidence of approximately 5% in the referent communities. Increases in similar respiratory symptoms were also observed in residents of communities where toxic waste containing high levels of hydrogen sulfide were illegally dumped in Côte d'Ivoire (Dongo et al. 2012), in residents living near sour gas/oil fields in southeast New Mexico (Kilburn et al. 2010), and in communities near swine feeding operations in east North Carolina (Schinasi et al. 2011). A positive association was found between 12-hour mean hydrogen sulfide atmospheric concentrations and the incidence of self-reported signs of respiratory effects (particularly runny nose, wheezing, and difficulty breathing and nasal irritation) (Schinasi et al. 2011).

Bhambhani and associates conducted a number of studies in young healthy volunteers exposed to hydrogen sulfide during exercise via a mouthpiece; the subjects were unable to smell the hydrogen sulfide and their eyes were not exposed to the gas. 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 were noted, but exposure to 5 ppm resulted in a significant increase in maximum oxygen uptake compared to controls. Since there were no alterations in maximum cardiac output, the study authors concluded that the increase in oxygen uptake was likely due to oxygen being utilized to oxidize sulfide to sulfate rather than an increase in the amount of oxygen being utilized by exercising muscles. 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 the partial pressure of oxygen, partial pressure of carbon dioxide, oxygen uptake, percentage of oxygen uptake, uptake of carbon dioxide and minute volume, or respiratory exchange ratio in male or female volunteers during 30 minutes of submaximal exercise (Bhambhani et al. 1994). Exposure to 10 ppm of hydrogen sulfide for 15 minutes during submaximal exercise did not result in significantly altered pulmonary

function test results in men and women (Bhambhani et al. 1996a) or changes in oxygen partial pressure, carbon dioxide partial pressure, oxygen saturation, or pH in men or women (Bhambhani et al. 1997). However, exposure to 10 ppm hydrogen sulfide did significantly reduce oxygen uptake, but had no effect on carbon dioxide uptake or minute volume. The magnitude in the decrease in oxygen uptake was small (5–18%), but was observed in ≥70% of the subjects.

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 (suggestive of bronchial obstruction). 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).

In a study of residents living near a hog manure lagoon, an increased frequency of shortness of breath while climbing stairs was observed when compared to residents living 3 km from the lagoons or residents living in another state. However, there were no increases in the frequency of shortness of breath while at rest or while walking (Kilburn 2012). Expiratory flows and vital capacity were also significantly decreased in the exposed residents; a higher incidence of chest tightness, dry mouth, and throat tightness was also reported. The hydrogen sulfide exposure levels were poorly quantified and the residents were likely exposed to other contaminants. The investigators noted that the levels of hydrogen sulfide in indoor air samples from 12 homes ranged from 0 to 2,100 ppb and that the levels of two outdoor samples were >1,000 ppb.

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: no hydrogen sulfide exposure, hydrogen sulfide exposure sufficient to produce symptoms, and hydrogen sulfide exposure high enough to cause unconsciousness (knockdown). 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% 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 treatment 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 smoked versus water treatment workers who smoked was 1.7 (95% CI=0.2–13.6).

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 (due to 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 (indicated by increased protein in nasal lavage fluids) was observed in animals exposed to airborne concentrations of 400 ppm; this condition resolved by 20 hours postexposure. The 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 were indicative of toxic effects on the pulmonary epithelium. In addition, pulmonary alveolar macrophages from animals exposed to 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 higher dose. Focal areas 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 a 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 epithelium 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 when 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.

In another study, bilaterally symmetrically, mild respiratory epithelial damage was also observed in rats exposed to 200 ppm hydrogen sulfide for 3 hours (Roberts et al. 2008). Infiltration with inflammatory cells was observed 3 hours postexposure, epithelial sloughing and loss of the basal cellular structure were observed 6 hours postexposure, and epithelial regeneration was observed at 24 hours postexposure. A complete recovery of the epithelial damage was observed after 5 consecutive days of exposure to 200 ppm for 3 hours/day (Roberts et al. 2008).

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). By 24 hours postexposure, cytochrome *c* oxidase activity had returned to normal for animals exposed to 200 ppm, but not for those exposed to 400 ppm. 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 lower concentration, mild perivascular edema was found. At the higher concentration, 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. Other studies found slight pulmonary congestion in male Wistar rats exposed to 75 ppm hydrogen sulfide for 1 hour (Kohno et al. 1991) and moderate-to-massive pulmonary edema in male F-344 rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990).

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.

In summary, short- and long-term studies in humans and animals provide strong evidence that the respiratory tract is a sensitive target of hydrogen sulfide toxicity. Studies in communities living near a source of hydrogen sulfide pollution have found increases in respiratory symptoms, particularly signs of nasal irritation, cough, and shortness of breath (Haahtela et al. 1992; Jaakkola et al. 1990; Legator et al. 2001; Marttila et al. 1995; Partti-Pellinen et al. 1996; Schinasi et al. 2011), worsening of asthma symptoms (Campagna et al. 2004; Carlsen et al. 2012),and alterations in lung function (Kilburn 2012). Occupational exposure studies have found altered lung function and increased odds of obstructive lung disease among sewer workers with presumed high exposure (Richardson 1995) and increased prevalence of shortness of breath and wheezing without an effect on lung function among oil and gas workers with the highest exposure to hydrogen sulfide (Hessel et al. 1997). A major limitation of the community and occupational exposure studies is the lack of reliable hydrogen sulfide exposure data and concomitant exposure to other substances, including other sulfur compounds and particulate matter. Human

experimental studies have not found alterations in lung function in exercising subjects exposed to 5 ppm for 16 or 30 minutes or 10 ppm for 15 minutes (Bhambhani and Singh 1991; Bhambhani et al. 1994, 1996a). A decrease in airway resistance and conductance was observed in 20% of asthmatics exposed to 2 ppm for 10 minutes, although the change in the whole group was not significantly different from controls (Jappinen et al. 1990). In rats, a 3- or 4-hour exposure to ≥200 ppm resulted in necrosis and exfoliation of the nasal respiratory and olfactory epithelial cells (Brenneman et al. 2002; Lopez et al. 1988b; Roberts et al. 2008); the NOAEL for these effects was 80 ppm (Brenneman et al. 2002). Exposure to ≥75 ppm for 1–4 hours resulted in pulmonary edema with increasing severity as exposure levels increased (Kohno et al. 1991; Lopez et al. 1988a; Prior et al. 1990). Repeated exposure to ≥30 ppm resulted in olfactory neuronal loss in the nasal cavity of rats and mice (Brenneman et al. 2000; CIIT 1983a, 1983b, 1983c; Dorman et al. 2004); the NOAEL was 10 ppm.

Carbonyl Sulfide. No studies were located regarding respiratory effects in humans after inhalation exposure to carbonyl sulfide.

Only one study has examined the respiratory tract in animals following inhalation exposure to carbonyl sulfide. No morphological alterations were observed in the lungs of rabbits continuously exposed to 54 ppm for 7 weeks (Kamstrup and Hugod 1979).

Cardiovascular Effects.

Hydrogen Sulfide. 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 (also referred to as an inverted P wave) likely indicative of an ectopic atrial rhythm was noted; 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 $\mu g/m^3$, with 35% of the measurements over 70 $\mu g/m^3$ and 10% over 400 $\mu g/m^3$ (Bates et al. 1997), the lack of monitoring information in the Bates et al. (1998) study 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% CI 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. Significant increases in serum cardiac enzyme levels (aspartate aminotransferase [AST], creatinine kinase, lactate dehydrogenase) and cardiac troponin I activity was observed in rats exposed to 300 ppm hydrogen sulfide for 60 minutes (Wu et al. 2011).

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).

Carbonyl Sulfide. No studies were located regarding cardiovascular effects in humans after inhalation exposure to carbonyl sulfide.

No morphological alterations were observed in the coronary arteries, aortic arch, descending thoracic aorta, or pulmonary arteries (Hugod and Astrup 1980; Kamstrup and Hugod 1979) and no myocardial ultrastructural changes (Hugod 1981) were found in rabbits continuously exposed to 54 ppm carbonyl sulfide for 7 weeks.

Gastrointestinal Effects.

Hydrogen Sulfide. 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 containing hydrogen sulfide, significant increases in nausea were 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. It was noted that the sulfur dioxide levels were the same at both the higher and lower hydrogen sulfide exposure levels. A significant increase in the incidence of reported nausea was found during the high exposure period (23%) as compared to the incidence during the low exposure period (5%). In the second 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).

Carbonyl Sulfide. No studies were located regarding gastrointestinal effects in humans or animals after inhalation exposure to carbonyl sulfide.

Hematological Effects.

Hydrogen Sulfide. 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 within the normal range 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 activity and erythrocyte protoporphyrin concentration were noted at the 2-hour and 1-week time periods, but not to the level of statistical 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). Laug and Draize (1942) reported increased sulfhemoglobin levels in rabbits exposed for at least 20 minutes to unspecified levels of hydrogen sulfide.

Carbonyl Sulfide. One study examined the potential of carbonyl sulfide to induce hematological alterations. In rats exposed to carbonyl sulfide for 11 days, significant increases in methemoglobin levels were observed at ≥151 ppm; however, the magnitude of the methemoglobin levels in treated animals (1.3–2.3% compared to 0.8–1.0% in controls) was low and was not considered toxicologically relevant.

Decreases in erythrocyte count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were observed in female rats exposed to 151 or 253 ppm, but were not observed at 453 ppm or in males. The lack of concentration-response and the finding in only one sex suggest that these alterations may not be related to carbonyl sulfide exposure.

Musculoskeletal Effects.

Hydrogen Sulfide. 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 decreases in muscle citrate synthase activity that was 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).

Carbonyl Sulfide. No studies were located regarding musculoskeletal effects in humans or animals after inhalation exposure to carbonyl sulfide.

Hepatic Effects.

Hydrogen Sulfide. A retrospective study of 221 gas and oil workers exposed to hydrogen sulfide measured unspecified liver enzyme activity in about 30% of the subjects exposed by inhalation to hydrogen sulfide (Burnett et al. 1977). The investigators noted that abnormalities were detected in several subjects; no additional information was provided.

No changes in serum protein, lactate dehydrogenase (LDH), serum glutamic-oxaloacetic transaminase (SGOT; also referred to as aspartate aminotransferase [AST]), or alkaline phosphatase activity 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).

Carbonyl Sulfide. No studies were located regarding hepatic effects in humans or animals after inhalation exposure to carbonyl sulfide.

Renal Effects.

Hydrogen Sulfide. Blood urea nitrogen and serum electrolyte levels were within the normal range 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, suggesting 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).

Carbonyl Sulfide. No studies were located regarding renal effects in humans or animals after inhalation exposure to carbonyl sulfide.

Endocrine Effects.

Hydrogen Sulfide. 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).

Carbonyl Sulfide. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to carbonyl sulfide.

Dermal Effects.

Hydrogen Sulfide. 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 (which may have been related to increased sulfhemoglobin levels) and erythema were noted in rabbits exposed to unspecified concentrations of hydrogen sulfide for 2 hours (Laug and Draize 1942).

Carbonyl Sulfide. No studies were located regarding dermal effects in humans or animals after inhalation exposure to carbonyl sulfide.

Ocular Effects.

Hydrogen Sulfide. 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 $\mu g/m^3$ (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 $\mu g/m^3$; 70 ppb), and not annual mean concentrations. The ocular effects may have also been due to co-exposure to methyl mercaptan and methyl sulfides. Methyl mercaptan is also an eye irritant and it was also present at an annual mean concentration of 2–5 $\mu g/m^3$ with the highest daily average concentration being 50 $\mu g/m^3$ (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 $\mu g/m^3$, with 35% of the measurements >70 $\mu g/m^3$ and 10% >400 $\mu g/m^3$ (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; $p=0.005$). In a subsequent study by this group in which the Rotorua residents were divided into three groups based on expected exposure levels, there was an increase in the incidence of disorders of the eye and adnexa (SIR=1.38; 95% CIs of 1.16–1.64) in the high exposure group when compared to the incidence in the low exposure group (Bates et al. 2002). The incidence in the medium exposure group was not significantly higher than the low exposure group. 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).

As noted previously, interpretation of the results of the Bates et al. (1997, 2002) studies is limited by the lack of concurrent monitoring data and examination of potential exposure to other compounds.

Ocular irritation has also been noted after animals were exposed to hydrogen sulfide. Epiphora was noted in F-344 rats exposed to 400 ppm,of hydrogen sulfide for 4 hours (Lopez et al. 1988b); effects were not observed at 200 ppm. 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).

Carbonyl Sulfide. No studies were located regarding ocular effects in humans or animals after inhalation exposure to carbonyl sulfide.

Body Weight Effects.

Hydrogen Sulfide. 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 statistically 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).

Carbonyl Sulfide. No studies were located regarding body weight effects in humans after inhalation exposure to carbonyl sulfide.

No alterations in body weight were observed in rats exposed to 453 ppm carbonyl sulfide for11 exposure days (Monsanto 1985b) or 182 ppm for 13 weeks (Monsanto 1987).

Metabolic Effects.

Hydrogen Sulfide. 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; no significant changes in the activities of muscle lactate dehydrogenase, citrate synthase, or cytochrome oxidase were observed.

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).

Carbonyl Sulfide. No studies were located regarding metabolic effects in humans after inhalation exposure to carbonyl sulfide.

Significant increases in serum cholesterol levels were observed in rabbits continuously exposed to 54 ppm carbonyl sulfide for 7 weeks (Kamstrup and Hugod 1979). However, the alterations were only observed at weeks 1, 6, and 7 and corresponded to a downward fluctuation in control levels. An increase in free cholesterol levels in the media layer of the aorta (but not in the intima or internal aspect of the media layer) was also observed; the investigators suggested that this increase was probably due to the increase in serum cholesterol levels.

3.2.1.3 Immunological and Lymphoreticular Effects

Hydrogen Sulfide. 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 to hydrogen sulfide in acute- and intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

Carbonyl Sulfide. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to carbonyl sulfide.

3.2.1.4 Neurological Effects

Hydrogen Sulfide. 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 recurring 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; 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; no abnormalities were noted in the head CT scan. 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, 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 (even 4 years later) including problems with general cognitive ability, motor function, and impaired performance on tests of cognitive function. Some of these symptoms appeared to be alleviated through a combined treatment with fairly high doses of Ritalin and Cyclert drugs that 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 screening 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 “knockdown” exposure had an even larger suite of deficit in cognitive function, 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 within normal limits. 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.

The acute toxicity of low levels of hydrogen sulfide was examined by Fiedler et al. (2008). In healthy young adults, exposure to 0.5 or 5 ppm hydrogen sulfide for 2 hours did not result in decrements in visual acuity or visual contrast sensitivity, cognitive tests, or postural sway. A decrease in performance on an auditory verbal learning test was observed as the duration increased, particularly in subjects exposed to 0.05 or 0.5 ppm, relative to the 5 ppm group; however, there was no relationship between exposure concentration and performance. The subjects reported an increase in anxiety during exposure to 5 ppm, which was related to odor irritation.

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.

A study of sewer workers (Farahat and Kishk 2010) also reported a significant increase in self-reported memory defects and lack of concentration; the mean hydrogen sulfide concentration inside of manhole openings was 9.4 ppm (range of 8.8–10.5 ppm). In function tests, significant alterations were observed in the test of auditory event-related potentials; simple reaction time; and figure, visual, verbal, and logical memory tests. However, no significant associations between performance on neurophysiological or neuropsychological tests and urinary thiosulfate levels (biomarker for hydrogen sulfide exposure) were found. The study did not specify when during the workshift the workers were tested; thus, it is not known whether the study evaluated acute or chronic neurotoxicity.

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 $\mu g/m^3$, the 24-hour concentrations varied between 0 and 56 $\mu g/m^3$, and the maximum 1-hour concentration was 155 $\mu g/m^3$; there was no TRS detected in the reference community. In the polluted community, the sulfur dioxide annual mean concentration was 1 $\mu g/m^3$, the 24-hour concentrations varied between 0 and 24 $\mu g/m^3$ and the maximum 1-hour concentration was 152 $\mu g/m^3$. In the reference community, the mean sulfur dioxide level was 1 $\mu g/m^3$ and the maximum 1-hour concentration was 30 $\mu g/m^3$. 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, sex, 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 $\mu g/m^3$, with 35% of the measurements >70 $\mu g/m^3$ and 10% >400 $\mu g/m^3$; 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 sex and ethnicity, the increased risks remained significant for all but non-Māori men. As noted previously, the percentage of Rotorua residents of Māori ethnicity is significantly higher than the rest of New Zealand. 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% CI) 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, the potential exposure to other compounds, 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 (e.g., 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.

A significant association between mood/stress ratings and hydrogen sulfide levels were reported in residents living within 1.5 miles of at least one industrial hog operation in North Carolina (Horton et al. 2009). The average hydrogen sulfide concentrations ranged from <0.01 to 1.5 ppb and the highest measured levels ranged from 2 to 90 ppb. During a 2-week period, the subjects were asked to go outside for 10 minutes twice a day and return inside and complete a five-question survey on mood/stress using a 9-point rating scale. Although most of the time (>80%) the subjects rated annoyance or stress as 0 (not at all), significant associations between reporting stress or annoyance and feeling nervous or anxious with hydrogen sulfide atmospheric levels were found. The ORs for a 1-ppb change in hydrogen sulfide were

1.18 (95% CI=1.08–1.30) for stress or annoyance and 1.12 (95% CI=1.08–1.30) for feeling nervous or anxious. Significant associations between the response to these questions and semivolatile PM_{10} levels were also found. It is unclear whether the observed effects were symptoms of a neurological effect or a response to the hydrogen sulfide odor.

Additional ecological studies have reported neurological effects in communities near industrial sources of hydrogen sulfide, but do not provide reliable monitoring data. Alterations in tests of balance sway with eyes open or closed, color discrimination, visual field performance, cognition, and reaction time were observed in residents living near a hog manure lagoon, as compared to an out-of-state control group (Kilburn 2012). In residents living near an industrial source emitting chronic, low levels of hydrogen sulfide, a significant increase in central nervous system effects (OR=12.7; 95% CI=7.59–22.09) was observed, as compared to referent communities (Legator et al. 2001). A number of central nervous system effects were reported by at least 40% of the residents (including fatigue, depression, short-term memory loss, difficulty sleeping, numbness, lethargy, headaches, and changes in senses); the incidences of these symptoms in the referent population were ≤10%. Neurological symptoms (headache, dizziness, lightheadedness, loss of balance, extreme fatigue, somnolence, insomnia, irritability, lack of concentration, recent and long-term memory loss, and instability of mood) were reported in residents living near sour gas/oil fields in New Mexico (Kilburn et al. 2010). Impaired performance on neurophysiological and neuropsychological function tests (including reaction time, balance sway, grip strength, psychological function, verbal recall, attention/coordination, and long-term memory) were also observed. In addition to the potential for exposure to hydrogen sulfide, the residents were also likely exposed to benzene, toluene, ethylbenzene, and xylenes (BTEX); cyclohexane; n-hexane; and naphthalene.

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).

A decreased response rate in a discriminated avoidance task was observed in male Wistar rats exposed to ≥200–300 ppm hydrogen sulfide (Higuchi and Fukamachi 1977). At concentrations of <400–500 ppm,

the response rates and percent avoidances recovered rapidly when ventilation with clean air was provided; at 400–500 ppm, the response rates were almost to within normal limits by the following day. When the 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). As with the discriminated avoidance task, the 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. The 5-week exposure to hydrogen sulfide 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 the 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 hydrogen sulfide studies are recorded in Table 3-1 and plotted in Figure 3-1.

The available human data, supported by animal studies, provide strong evidence that hydrogen sulfide exposure adversely affects the nervous system. The most commonly reported effect in humans is unconsciousness which can be followed by death or an apparent full recovery (Deng and Chang 1987; Krekel 1964; McDonald and McIntosh 1951; Milby 1962; Spolyar 1951). Although the individual appears to recover from the exposure, subsequent studies have found permanent neurological effects in some of the subjects, including vision and memory impairment, reduced motor function, and abnormal learning function (Kilburn 1993, 1997; Schneider et al. 1998; Snyder et al. 1995; Tvedt et al. 1991a, 1991b). No reliable data on the exposure level resulting in unconsciousness were located. Subclinical

neurological effects (detected as alterations in neurological tests) were reported in individuals chronically exposed to low (concentration not specified) levels of hydrogen sulfide (Farahat and Kishk 2010; Kilburn 1997); the effects included alterations in balance, reaction time, verbal recall, and memory. Additionally, workers and community members living in areas with hydrogen sulfide pollution reported fatigue, irritability, headaches, poor memory, and/or stress (Ahlborg 1951; Horton et al. 2009; Kilburn et al. 2010; Legator et al. 2001; Partti-Pellinen et al. 1996). As with other studies, limited monitoring data are available and the subjects were exposed to other substances including other sulfur compounds, benzene, toluene, and/or particulate matter. Studies in animals confirm the findings from the human studies. Unconsciousness was observed in rabbits exposed to 72 ppm for 1.5 hours (Kosmider et al. 1967) and rats exposed to 800 ppm for 20 minutes (Beck et al. 1979) and lethargy was observed in rats exposed to 400 ppm for 4 hours (Lopez et al. 1988b). Additionally, impaired learning was observed in rats exposed to 125 ppm 4 hours/day, 5 days/week for 11 weeks (Partlo et al. 2001). In other intermediate-duration studies, no effects on posture, gait, or reflexes were observed in rats and mice exposed to 80 ppm 6 hours/day, 5 days/week for 90 days (CIIT 1983a, 1983c).

Carbonyl Sulfide. No studies were located regarding neurological effects in humans after inhalation exposure to carbonyl sulfide.

Acute- and intermediate-duration exposure studies clearly identify the nervous system as a sensitive target of carbonyl sulfide toxicity. Morgan et al. (2004) noted a number of effects in rats exposed to carbonyl sulfide 6 hours/day, 5 days/week for 12 exposures. Hypotonia and slight gait abnormalities were observed in rats exposed to 400 ppm and ataxia and hypothermia were observed at 500 ppm. Hypothermia was also observed after one or two exposures to 600 ppm. Immediately after a single 6-hour exposure to 600 ppm, lethargy was noted in rats; 1 day postexposure, the animals exhibited clinical signs of hypothermia, lethargy, head tilt, and ataxia (Morgan et al. 2004). Although the clinical signs lessened over a 14-day recovery period, ataxia with head tilt was noted in several animals at the end of the recovery period. Another study also reported ataxia in rats exposed to 453 ppm 6 hours/day, 5 days/week for at least 6 days (Monsanto 1985b). No overt signs of neurotoxicity were observed in rats exposed to 300 ppm 6 hours/day, 5 days/week for 4 or 12 exposures (Morgan et al. 2004) or 253 ppm 6 hours/day, 5 days/week for 11 exposures (Monsanto 1985b). Exposure to 400 ppm (6 hours/day, 5 days/week) for 10 or 12 exposures also resulted in decreases in motor activity (Herr et al. 2007) and forelimb and hindlimb grip strength (Herr et al. 2007; Morgan et al. 2004); no alterations in motor function were observed at 300 ppm (Herr et al. 2007; Morgan et al. 2004). Functional observational battery testing in rats exposed to 400 ppm for 12 weeks showed mild gait changes in about 25% of the

rats, which was more prevalent after 6 weeks of exposure than after 12 weeks of exposure (Morgan et al. 2004). Morgan et al. (2004) suggested that there was some compensation for the motor impairment since the effects were more pronounced after 2 weeks of exposure than after 12 weeks of exposure.

Histopathological alterations were observed in rats following a single 6-hour exposure to 600 ppm carbonyl sulfide (Morgan et al. 2004). Two weeks after the exposure, necrosis and microgliosis was observed in the cerebellar nucleus, internal capsule, and thalamus; no histological alterations were observed in the brains of rats similarly exposed to 75–300 ppm. In rats sacrificed in moribund condition after 2 days of exposure to 600 ppm (6 hours/day), bilateral symmetrical necrosis in the parietal cortex area 1 and thalamus and necrosis in the retrosplenial granular cortex, pyriform cortex, red nucleus, cerebellar roof nucleus, posterior collicular nucleus, and anterior olivary nucleus were observed (Morgan et al. 2004; Sills et al. 2004). No morphological lesions were observed in the brains of rats exposed to 500 ppm 6 hours/day for 1 or 2 days (Morrison et al. 2009). After 3 or 4 days of exposure, bilateral symmetrical necrosis was observed in the posterior colliculi. Necrosis was also observed in the frontoparietal cortex, putamen, retrosplenial cortex, thalamus, and anterior olivary nucleus in rats exposed to 500 ppm for 4 days. After 5 days of exposure, neuronal degeneration was observed in the posterior colliculi; it was also observed in the medial geniculate nucleus, parietal cortex, and caudate/putamen after 10 days of exposure (Morrison et al. 2009). Neuronal loss and microgliosis were observed in the posterior thalamic nuclear group, zona inserta of the hypothalamus, and posterior colliculus (Sills et al. 2004). Exposure to 400 ppm 6 hours/day, 5 days/week for 12 exposures resulted in bilateral symmetrical necrosis in the parietal cortex area 1 and putamen (Morgan et al. 2004). Exposure to 500 ppm also resulted in bilateral symmetrical necrosis in the retrosplenial cortex, thalamus, posterior colliculus, and anterior olivary nucleus; additionally, there was cavitation (loss of brain substance) within the parietal cortex and retrosplenial cortex, as compared to rats exposed to 500 ppm for 5 days. No significant increases in the incidence of histological alterations were observed in rats exposed to 300 ppm for 12 exposures (Morgan et al. 2004).

Similar findings were observed in rats exposed to 400 ppm carbonyl sulfide 6 hours/day, 5 days/week for 12 weeks (Morgan et al. 2004; Sills et al. 2004). Significant increases in the incidence of unilateral or bilateral symmetrical cortical necrosis and cavitation in the parietal cortex area 1 and bilateral neuronal loss with microgliosis of the posterior colliculus were observed. No histological alterations were observed in rats exposed to 300 ppm. The results of the acute and intermediate duration studies suggest that the histological damage occurs shortly after exposure initiation and does not worsen with continued exposure.

Neurophysiological alterations that correlated with the histopathological damage were also observed in rats exposed to 400 ppm carbonyl sulfide 6 hours/day, 5 days/week. After 12 weeks of exposure, significant increases in the peak-to-peak amplitudes in somatosensory evoked potentials from the S1 facial region cortex were observed. Significant alterations in peak amplitudes in brainstem auditory-evoked responses were observed after 2 (Herr et al. 2007; Morgan et al. 2004) or 12 weeks of exposure (Herr et al. 2007); no alterations were observed in rats exposed to 300 ppm for 12 weeks (Herr et al. 2007). The investigators noted that the observed alterations of brainstem auditory-evoked responses peak generation indicated alterations in the region of the olivary complex-lateral lemniscus region of the brainstem, but with normal function of the auditory nerve and cochlear nucleus region. Additionally, the decreased peak amplitudes and lack of change in the peak latencies is suggestive of loss of neurons rather than changes in conduction along the brainstem neural pathway. Studies by Morgan et al. (2004) and Sills et al. (2004) have demonstrated neuronal loss and microglial infiltration in the posterior colliculi and anterior olivary nuclei in rats exposed to 400 ppm for 4–12 weeks.

Reflex modification of audiometry or visual evoked potentials after 10 exposures (6 hours/day, 5 days/week, testing conducted 11 days postexposure) and peripheral nerve action potential or nerve conduction velocity after 10 exposures (tested 27 days postexposure) or 12 weeks of exposure (6 hours/day, 5 days/week; tested 34–40 days postexposure) were not significantly altered in rats exposed to 400 ppm (Herr et al. 2007). Additionally, there were no alterations in nerve conduction velocity after 10 exposures or 12 weeks of exposure (Herr et al. 2007).

The highest NOAEL values and all reliable LOAEL values for neurological effects following exposure to carbonyl sulfide are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.1.5 Reproductive Effects

Hydrogen Sulfide. 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

Table 3-2 Levels of Significant Exposure to Carbonyl 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 (CD)	4 hr				1111 M (LC50)	DuPont 1981	
2	Rat (Sprague-Dawley)	4 hr				1082 (LC50)	Monsanto 1985a	
Systemic								
3	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 11 exposures	Hemato	453			Monsanto 1985b	
			Bd Wt	453				
Neurological								
4	Rat (Fischer- 344)	6 hr/d 5 d/wk 10 exposures		300 M	400 M (decreased motor activity, grip strength, slightly abnormal gait)		Herr et al. 2007	
5	Rat (Sprague-Dawley)	6 hr/d 5 d/wk 11 exposures		253		453 (ataxia, tremors, convulsions)	Monsanto 1985b	
6	Rat (Fischer- 344)	6 hr/d 4 d		300 M		600 M (hypothermia, ataxia, and necrosis in parietal cortex, thalamus, posterior colliculi)	Morgan et al. 2004	

Table 3-2 Levels of Significant Exposure to Carbonyl 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
7	Rat (Fischer- 344)	6 hr/d 5 d/wk 12 exposures		300	400	(decreased grip strength, hypotonia, slight gait abnormalities, necrosis in parietal cortex and putamen)	500	(hypothermia, lethargy, ataxia, necrosis of in parietal cortex, putamen, thalamus, and loss of brain substance in parietal cortex and retrosplenial cortex)	Morgan et al. 2004	
8	Rat (Fischer- 344)	6 hr/d 5 d					500 M	(neuronal degeneration in posterior colliculi)	Morrison et al. 2009	
9	Rat (Fischer- 344)	6 hr/d 10 d			500 M	(neuronal degeneration in posterior colliculi, medial geniculate nucleus, parietal cortex, and caudate/putamen)			Morrison et al. 2009	
10	Rat (Fischer- 344)	6 hr/d 1-2 d		500 M					Morrison et al. 2009	
11	Rat (Fischer- 344)	6 hr/d 3 d			500 M	(bilateral symmetrical necrosis in posterior colliculi)			Morrison et al. 2009	

Table 3-2 Levels of Significant Exposure to Carbonyl 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
12	Rat (Fischer- 344)	6 hr/d 4 d			500 M (necrosis in posterior colliculi, frontoparietal cortex, putamen, retrosplenial cortex, thalamus, and anterior olivary nucleus)		Morrison et al. 2009	
13	Rat (Fischer- 344)	6 hr/d 2 d			600 (Neuronal loss and microgliosis in posterior thalamic nuclear group, zona inserta of the hypothalamus, and posterior colliculus)		Sills et al. 2004	
INTERMEDIATE EXPOSURE								
Death								
14	Rabbit (White Danish Country)	continuous 7 weeks				54 M (3/8 died within first 5 days)	Hugod and Astrup 1980; Hugod 1981	
15	Rabbit (White Danish country)	continuous 7 weeks				54 F (3/18 died within 5 days)	Kamstrup and Hugod 1979	
Systemic								
16	Rabbit (White Danish Country)	continuous 7 weeks	Cardio	54 M			Hugod and Astrup 1980; Hugod 1981	

Table 3-2 Levels of Significant Exposure to Carbonyl 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
17	Rabbit (White Danish country)	continuous 7 weeks	Resp	54 F					Kamstrup and Hugod 1979	
			Cardio	54 F						
Neurological										
18	Rat (Fischer- 344)	6 hr/d 5 d/wk 12 wk		300	400	(altered somatosensory evoked potentials in the facial region cortex of the brain and brainstem auditory evoked response peaks)			Herr et al. 2007	
19	Rat (Fischer- 344)	6 hr/d 5 d/wk 12 wk		300	400	(necrosis or cavitation in parietal cortex and neuronal loss or microgliosis in posterior colliculus)			Morgan et al. 2004	
20	Rat (Fischer- 344)	6 hr/d 5 d/wk 12 wk		300			400	(microgliosis in the posterior colliculus, gliosis in the anterior olivary nucleus, bilateral symmetrical malacia in parietal cortex)	Sills et al. 2004	
Reproductive										
21	Rat (Sprague-Dawley)	6 hr/d 5 d/wk for 10 wk then 7 d/wk for 3 wk		60 M	182 M	(decreased pregnancy rate)			Monsanto 1987	

a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = Female; Hemato = hematological; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; ppm = parts per million; Resp = respiratory; wk = week(s)

Figure 3-2 Levels of Significant Exposure to Carbonyl Sulfide - Inhalation

Acute (≤14 days)

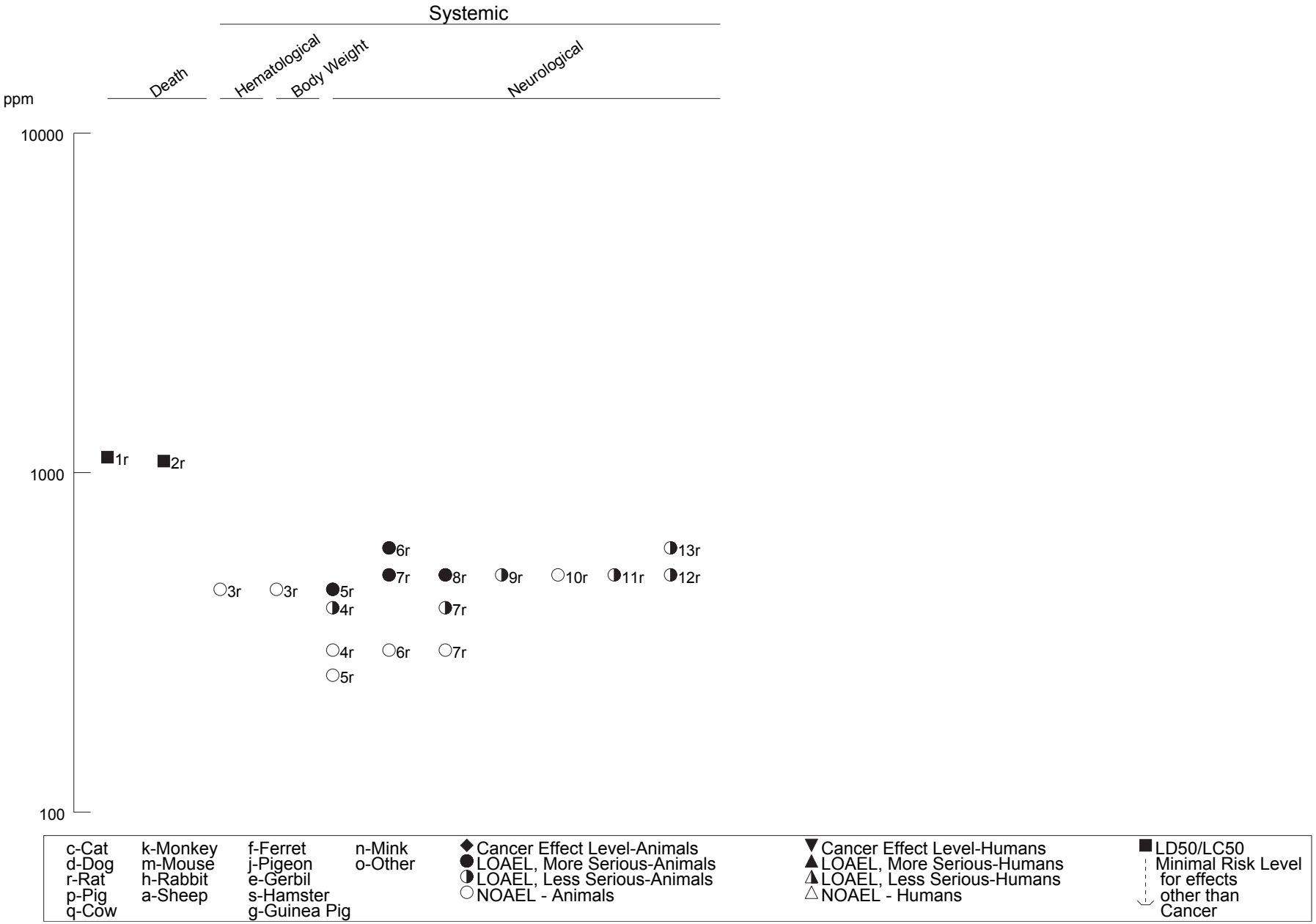
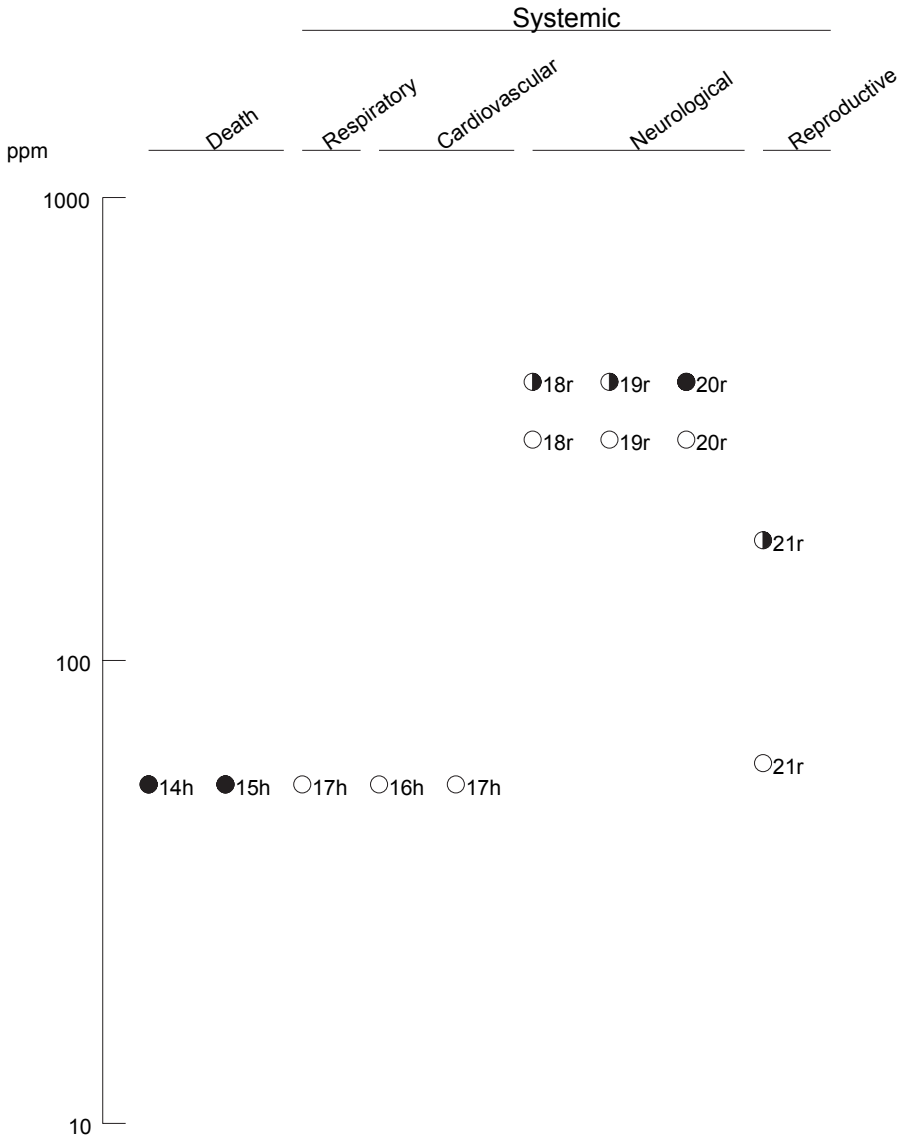


Figure 3-2 Levels of Significant Exposure to Carbonyl Sulfide - Inhalation *(Continued)*

Intermediate (15-364 days)



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

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 is limited by the lack of control of other potential confounding variables, particularly occupational exposure to other chemicals. 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 following exposure to hydrogen sulfide in rats and mice from intermediate-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

Carbonyl Sulfide. No studies were located regarding reproductive effects in humans after inhalation exposure to carbonyl sulfide.

One study examined the reproductive toxicity of carbonyl sulfide in male rats (Monsanto 1987). A decrease in pregnancy rate was observed in unexposed female rats mated with male rats exposed to 182 ppm carbonyl sulfide 6 hours/day, 5 days/week for 10 weeks and 6 hours/day, 7 days/week for a 3-week mating period. When the males were allowed to recover for 10 weeks prior to mating to unexposed females, no alterations in fertility were observed (Monsanto 1987). This study identified a NOAEL of 60 ppm. The NOAEL and the LOAEL values from this study are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.1.6 Developmental Effects

Hydrogen Sulfide. 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 activity 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 pinnae 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. Significant increases in serotonin levels were observed in the frontal cortex and cerebellum on postpartum days 14 and 21 in the 75 ppm group and in the cerebellum on postpartum day 21 in the 20 ppm group. Significant decreases in norepinephrine levels were observed in frontal cortex and cerebellum on postpartum day 14 in the 20 ppm group and in the frontal cortex on postpartum day 21 in the 20 ppm group. In contrast, significant increases in norepinephrine levels were observed in the cerebellum on postpartum day 7 in the 20 and 75 ppm groups, in the cerebellum on postpartum day 14 in the 75 ppm group, and in the frontal cortex and cerebellum on postpartum day 21 in the 75 ppm group (Skrajny et al. 1992). In a subsequent study using the same exposure regimen (i.e., between day 5 postcoital until day 21 postnatal) was used to follow the monoamine levels in various regions of the brain up to 60 days postnatal (Roth et al. 1995). This study 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.

Carbonyl Sulfide. No studies were located regarding developmental effects in humans or animals after inhalation exposure to carbonyl sulfide.

3.2.1.7 Cancer

Hydrogen Sulfide. 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 $\mu g/m^3$, with 35% of the measurements over 70 $\mu g/m^3$ and 10% over 400 $\mu g/m^3$ (Bates et al. 1997). Based on the cancer registry information, a significantly increased risk of nasal cancers (SIR=3.17; p=0.01) was found 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 Māoris than the rest of New Zealand, the investigators 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 Māoris in Rotorua as compared to female Māoris 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.

Carbonyl Sulfide. No studies were located regarding cancer effects in humans or animals after inhalation exposure to carbonyl sulfide.

3.2.2 Oral Exposure

No studies were located regarding health effects in humans or animals after oral exposure to carbonyl sulfide.

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

No studies were located regarding health effects in humans or animals after dermal exposure to carbonyl sulfide.

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 the 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 2011).

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

Hydrogen Sulfide. No studies were located regarding the genotoxicity of hydrogen sulfide in humans.

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.

Carbonyl Sulfide. No studies were located regarding the genotoxicity of carbonyl sulfide.

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 hydrogen sulfide is thiosulfate, which may further converted to sulfate and subsequently be 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.

Limited data on the toxicokinetics of carbonyl sulfide were located. Carbonyl sulfide is absorbed via the respiratory tract based on the finding of histological damage in the brains of rats exposed to carbonyl sulfide gas (Morgan et al. 2004). *In vitro* studies suggest that carbonyl sulfide is metabolized to hydrogen sulfide and thiosulfate (Chengelis and Neal 1979) and *in vivo* evidence suggests that it is metabolized by carbonic anhydrase (Chengelis and Neal 1980) and the mixed function oxidase enzyme system to carbon dioxide (Chengelis and Neal 1979). No additional toxicokinetic data were identified.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Hydrogen Sulfide. 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 demonstrate that absorption of hydrogen sulfide via the lungs occurs readily and rapidly, but 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.

Carbonyl Sulfide. No data on the absorption of carbonyl sulfide were identified; however, the findings of brain lesions in rats exposed to carbonyl sulfide gas provide evidence that it is absorbed via the respiratory tract.

3.4.1.2 Oral Exposure

Hydrogen Sulfide. Hydrogen sulfide exists as a gas; therefore, oral exposure to hydrogen sulfide will not typically 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).

Carbonyl Sulfide. As with hydrogen sulfide, carbonyl sulfide is a gas and oral exposure will not typically occur.

3.4.1.3 Dermal Exposure

Hydrogen Sulfide. 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. In one study, the 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 the head) to unknown concentrations of hydrogen sulfide (Walton and Witherspoon 1925).

Carbonyl Sulfide. No information was located on the dermal absorption of carbonyl sulfide.

3.4.2 Distribution

No information was located on the distribution of carbonyl sulfide by any route of exposure.

3.4.2.1 Inhalation Exposure

Hydrogen Sulfide. Few human data are available regarding tissue distribution after inhalation exposure to hydrogen sulfide. One case study reported sulfide (as bis[pentafluorobenzyl]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. At 24 hours after death, the blood sulfide 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 and colleagues 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, postmortem, in the 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). In another study of a man who was "overcome" by hydrogen sulfide in a tank, hydrogen sulfide levels of 0.92, 1.06, 0.34, and 0.38 μg/g were measured postmortem in the blood, brain, kidney, and liver, respectively (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 sulfide concentrations in tissues of 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 tissue distribution of hydrogen sulfide irrespective of duration: 10 μg/mL in blood, 25 μg/g in brain, 20 μg/g in lung, 37 μg/g in heart, 20 μg/g in liver, 25 μg/g in spleen, and 30 μg/g in 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.

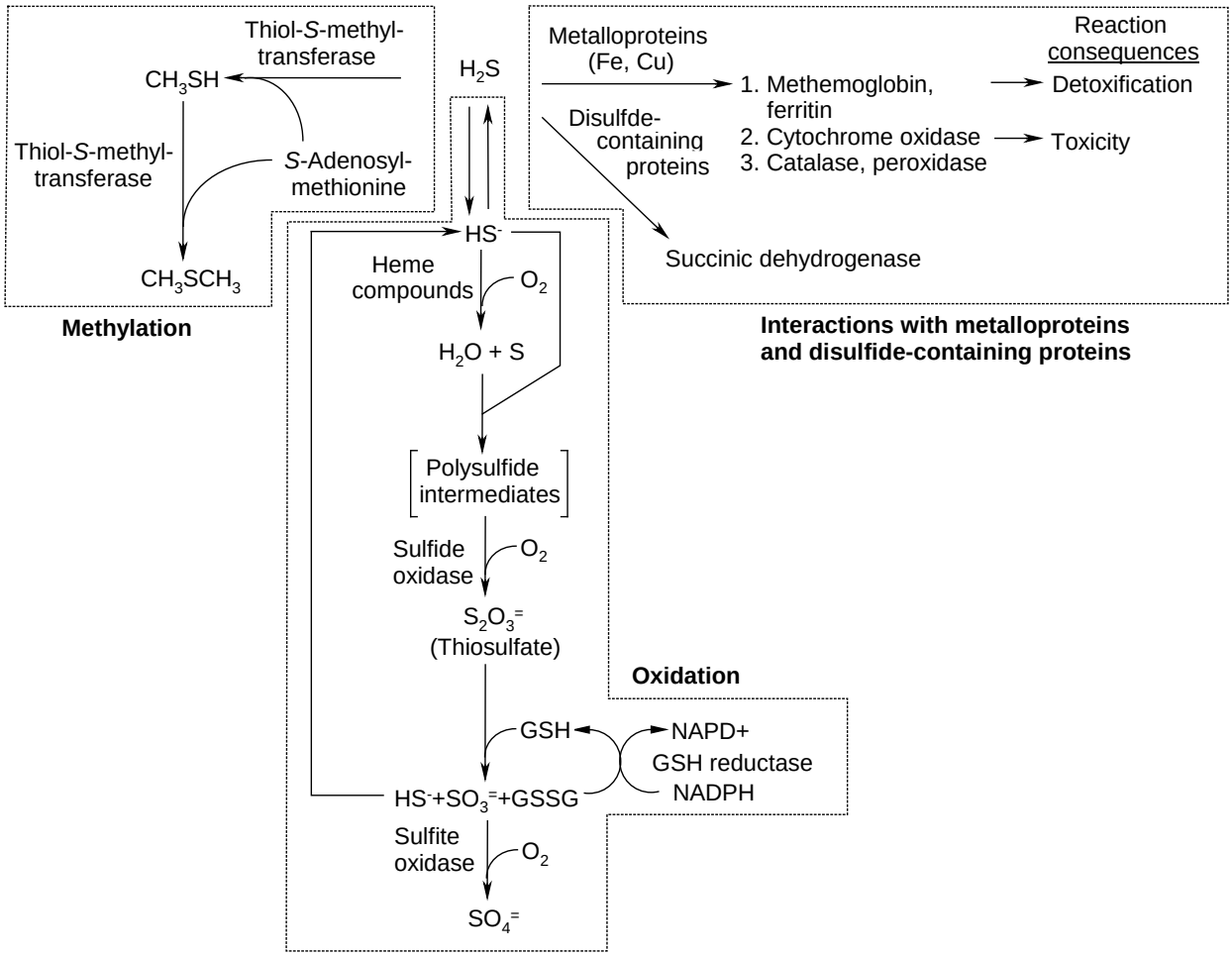
3.4.3 Metabolism

Hydrogen Sulfide. Hydrogen sulfide metabolism occurs through three pathways: oxidation, methylation, and reaction with metallo- or disulfide-containing proteins (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 3-3 and include oxidation, 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 can be further 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). 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 acts as an intermediate in the oxidation to sulfate (Bartholomew et al. 1980).

Figure 3-3. Metabolic Pathways of Hydrogen Sulfide



Source: Adapted from Beauchamp et al. 1984

Elevated levels of thiosulfate were observed in the blood, lung, and brain of Japanese white rabbits exposed to 500–1,000 ppm hydrogen sulfide (lethal concentration) for 14–30 minutes (Kage et al. 1992). Exposure to 100–200 ppm for 60 minutes resulted in thiosulfate levels in the urine that peaked (1.2 μM/mL) 1–2 hours after exposure and could still be detected in urine 24 hours after exposure (Kage et al. 1992). In the blood, the thiosulfate levels peaked (0.061 μM/mL) immediately after exposure and were undetectable after 4 hours. Sulfide was not detected in blood or urine of rabbits exposed to 100–200 ppm hydrogen sulfide.

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 activity in cecal and colonic mucosa, liver, lung, and kidney tissues. Thiol *S*-methyltransferase activity 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.

Carbonyl Sulfide. There are limited data on the metabolism of carbonyl sulfide. *In vitro* studies demonstrated that carbonyl sulfide was primarily metabolized by carbonic anhydrase to form hydrogen sulfide and thiosulfate (Chengelis and Neal 1979). Pre-exposure to acetazolamide (a carbonic anhydrase inhibitor) resulted in a decrease in mortality in rats exposed via intraperitoneal injection to a lethal dose of carbonyl sulfide (Chengelis and Neal 1980). There is also *in vitro* evidence that carbonyl sulfide is metabolized by the mixed-function oxidase enzyme system to carbon dioxide (Chengelis and Neal 1979; Dalvi et al. 1975). However, the metabolism was not inhibited by the cytochrome P-450 monooxygenase inhibitors (SKF 525-A, 4-methylpyrazole, metyrapone) or substrate (carbon disulfide) (Chengelis and Neal 1979).

3.4.4 Elimination and Excretion

No information was located on the elimination and excretion of carbonyl sulfide.

3.4.4.1 Inhalation Exposure

Hydrogen Sulfide. 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 measurements in 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 a slightly higher level than that of controls (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

Hydrogen Sulfide. 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. The trunk fur of rabbits was clipped and left intact or abraded for exposure to hydrogen sulfide gas (unknown concentrations) for 1.5–2 hours (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.

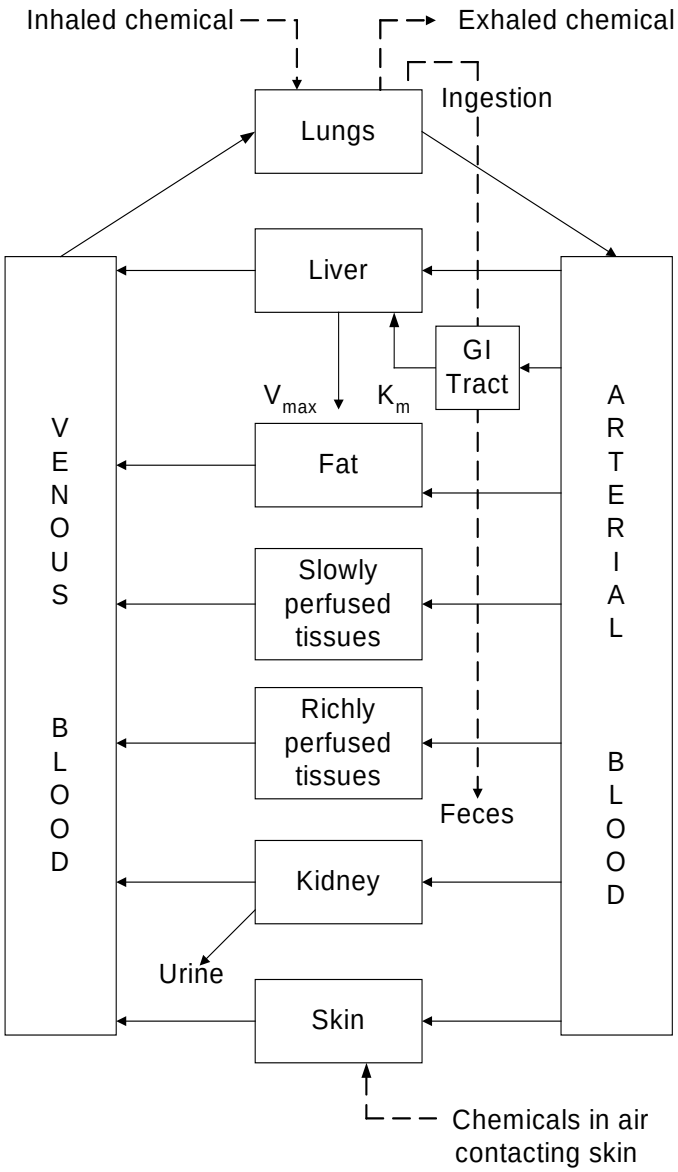
The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many 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 3-4 shows a conceptualized representation of a PBPK model.

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

No PBPK models have been developed for hydrogen sulfide or carbonyl sulfide.

Figure 3-4. 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.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Hydrogen Sulfide. 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 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.

Carbonyl Sulfide. No information was located on the pharmacokinetic mechanisms of carbonyl sulfide.

3.5.2 Mechanisms of Toxicity

Hydrogen Sulfide. 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 exposure to 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 neurotoxicity associated with hydrogen sulfide "knockdown" 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 was 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, 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).

Carbonyl Sulfide. No information was located on the mechanisms of carbonyl sulfide toxicity.

3.5.3 Animal-to-Human Extrapolations

Hydrogen Sulfide. 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 insignificant 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.

Schroeter and associates have used a toxicokinetic-driven computational fluid dynamics model to quantitatively predict hydrogen sulfide tissue doses in rats and humans (Schroeter et al. 2006a, 2006b). The computational fluid dynamics model is based on anatomically accurate representations of the geometry of the rat and human nasal cavities and rat nasal flux (uptake of hydrogen sulfide by the nasal tissue). Using the model, Schroeter et al. (2006a) predicted hydrogen sulfide dosimetry in the human nasal passage and derived regression equations that predicted the maximum and 99^{th} percentile flux values in the human olfactory region at hydrogen sulfide concentrations ranging from 1 to 50 ppm.

Carbonyl Sulfide. No human data for carbonyl sulfide were identified. There are limited data to compare the toxicity of carbonyl sulfide in different animal species since most of the toxicity studies examined rats. In rabbits, 17% mortality was observed following continuous exposure to 54 ppm for 5 days (Hugod 1981; Hugod and Astrup 1980; Kamstrup and Hugod 1979). The lowest lethal concentration in rats was 600 ppm; at this concentration, rats exposed 6 hours/day for 2 days were

sacrificed in moribund condition (Morgan et al. 2004). No deaths were observed in rats exposed to 500 ppm 6 hours/day, 5 days/week for 12 exposures (Morgan et al. 2004). The highest nonlethal concentration and the lethal concentration in rats adjusted for intermittent exposure (6 hours/24 hours) are 125 and 150 ppm, respectively. Although the lethal concentration in rabbits is lower than the highest nonlethal concentration in rats, the two studies are not directly comparable due to the differences in exposure duration. In the absence of information to the contrary, it is assumed that the rat is a suitable model for human toxicity to carbonyl sulfide.

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 or carbonyl sulfide to disrupt the function of the neuro-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 fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at

this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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).

Hydrogen Sulfide. 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.

Using computational fluid dynamics modeling, Schroeter et al. (2010) evaluated whether differences in nasal anatomy and ventilation between adults and children would effect hydrogen sulfide dosimetry in the olfactory region of the nasal cavity (see Section 3.5.3 for more information on the computational fluid dynamics model). Using data for five adults and two children, the study found that the interindividual differences in hydrogen sulfide uptake was <1.2.

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, alterations in performance on developmental neurobehavioral tests, or alterations in 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.

Carbonyl Sulfide. No information was located to evaluate children's susceptibility to carbonyl sulfide.

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).

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 and carbonyl 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 [DNA] adducts). Biomarkers of effect caused by hydrogen sulfide and carbonyl 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 and Carbonyl Sulfide

Hydrogen Sulfide. The most frequently used biomarker of hydrogen sulfide exposure is urinary thiosulfate 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 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 thiosulfate levels, a relationship between airborne hydrogen sulfide levels and blood sulfide levels has not been established; additionally, the biomarker is not specific to hydrogen sulfide.

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. The activity 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.

Carbonyl Sulfide. No information on biomarkers of exposure was identified for carbonyl sulfide.

3.8.2 Biomarkers Used to Characterize Effects Caused by Hydrogen Sulfide and Carbonyl Sulfide

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.

Carbonyl Sulfide. No information on biomarkers used to characterize effects caused by carbonyl sulfide was located.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Hydrogen Sulfide. 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-thiazolidine-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 using potentially fatal doses of both ethanol and hydrogen sulfide is unclear.

Carbonyl Sulfide. No studies examining interactions of carbonyl sulfide with other chemicals were located.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Hydrogen Sulfide. Some asthmatics exposed to 2 ppm hydrogen sulfide for 30 minutes had changes in pulmonary function tests suggestive 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. However, there are no data to support whether individuals with ulcerative colitis are more susceptible to the toxicity of hydrogen sulfide.

Carbonyl Sulfide. No information was located which could be used to identify populations that may be unusually susceptible to the toxicity of carbonyl sulfide.

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 and carbonyl sulfide. 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 and carbonyl sulfide. When specific exposures have occurred, poison control centers and medical specialists with experience and expertise in treating patients exposed or potentially exposed to hydrogen sulfide or carbonyl sulfide (i.e., board certified medical toxicologists, board certified occupational medicine physicians, pediatric environmental health medical specialists, etc.) should be consulted for medical advice. The following texts provide specific information about treatment following exposures to hydrogen sulfide:

Goldfrank LR, Howland MA, Flomenbaum NL, et al., eds. 2002. Goldfrank's toxicologic emergencies, 7th edition. New York, NY: McGraw Hill, 1505-1510.

Caravati EM. 2004. Hydrogen sulfide. In: Dart RC, ed. Medical toxicology, 3rd edition; Philadelphia, PA: Lippincott Williams and Wilkins, 1169-1174.

Guidotti TL. 2007. Hydrogen sulfide. In: Shannon MW, Borron SW, Burns MJ, Eds. Haddad and Winchester's clinical management of poisoning and drug overdose, 4th edition. Philadelphia, PA: Saunders Elsevier, 1335-1342.

3.11.1 Reducing Peak Absorption Following Exposure

There are no specific methods available to reduce the absorption of hydrogen sulfide or carbonyl sulfide following exposure. Supportive treatment includes removal from exposure, 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 or carbonyl sulfide.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Hydrogen Sulfide. 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 anecdotal 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). However, this treatment approach has only been shown to be effective if administered within the first minutes of exposure because the sulfide-methemoglobin complex breaks down rapidly in the presence of oxygen (Beck et al. 1981; Ellenhorn 1997; Hall 1996). Given the increased sensitivity of young children to the development of methemoglobinemia from exposure to nitrates/nitrites, care should be taken in using this approach. Consultation with a medical specialist with both expertise and experience treating pediatric patients exposed to hydrogen sulfide would be prudent.

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). Several case studies have reported the successful use of hyperbaric oxygen treatment (Asif and Exline 2012; Belley et al. 2005; Lindenmann et al. 2010). A study in rats found that hyperbaric treatment for 100 minutes initiated within 20 minutes of termination of a 60-minute exposure to 300 ppm hydrogen sulfide did not significantly alter partial pressure of oxygen, as compared to animals similarly exposed and not undergoing hyperbaric treatment (Wu et al. 2011). However, it did result in a significant decrease in lung cytochrome c oxidase levels. Use of hyperbaric oxygen therapy for hydrogen sulfide toxicity in pediatric populations needs further investigation.

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.

Carbonyl Sulfide. No information on interfering with the mechanisms of carbonyl sulfide toxicity was located.

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 and carbonyl 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 and carbonyl 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 and Carbonyl Sulfide

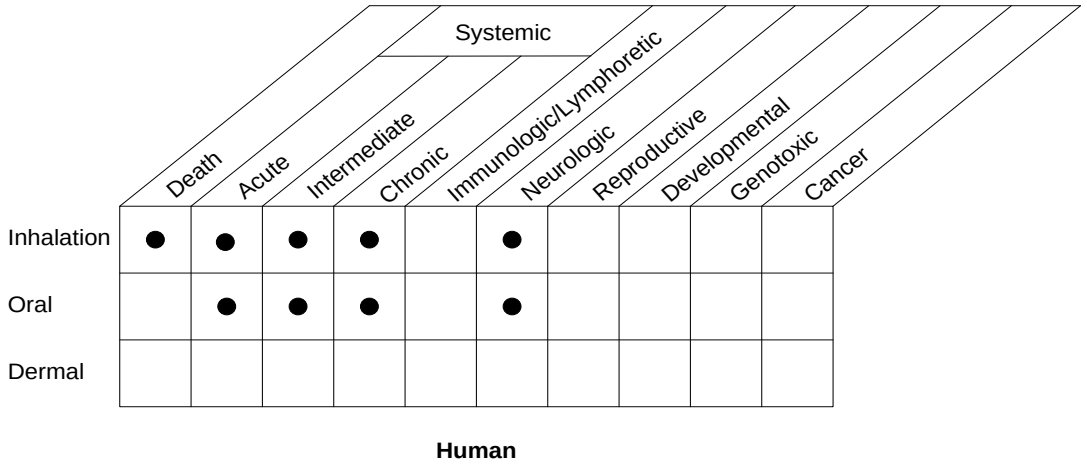
The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to hydrogen sulfide and carbonyl sulfide are summarized in Figures 3-5 and 3-6. The purpose of this figure is to illustrate the existing information concerning the health effects of hydrogen sulfide and carbonyl 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.

3.12.2 Identification of Data Needs

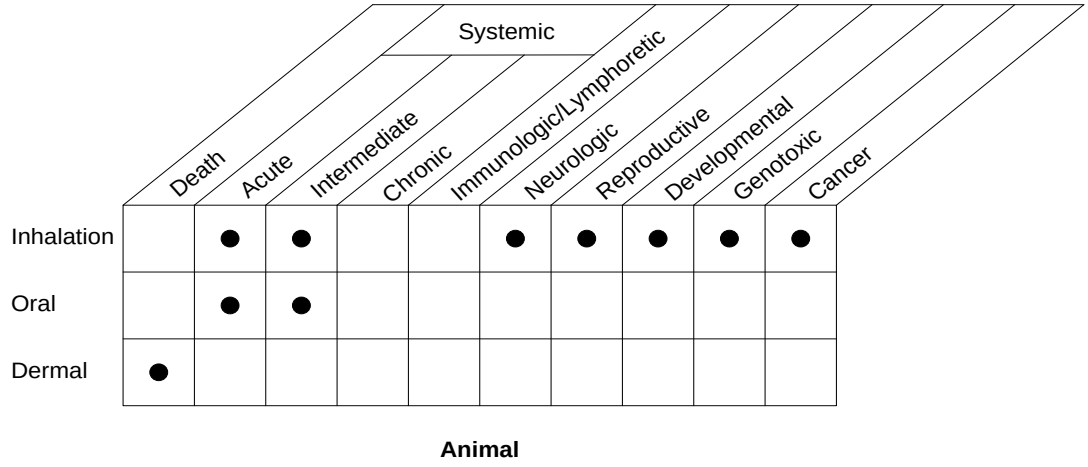
Acute-Duration Exposure.

Hydrogen Sulfide. There are numerous case reports of human fatalities (Adelson and Sunshine 1966; Ago et al. 2008; Allyn 1931; Bott and Dodd 2013; Breysse 1961; Christia-Lotter et al. 2007; Campanya et

Figure 3-5. Existing Information on Health Effects of Hydrogen Sulfide



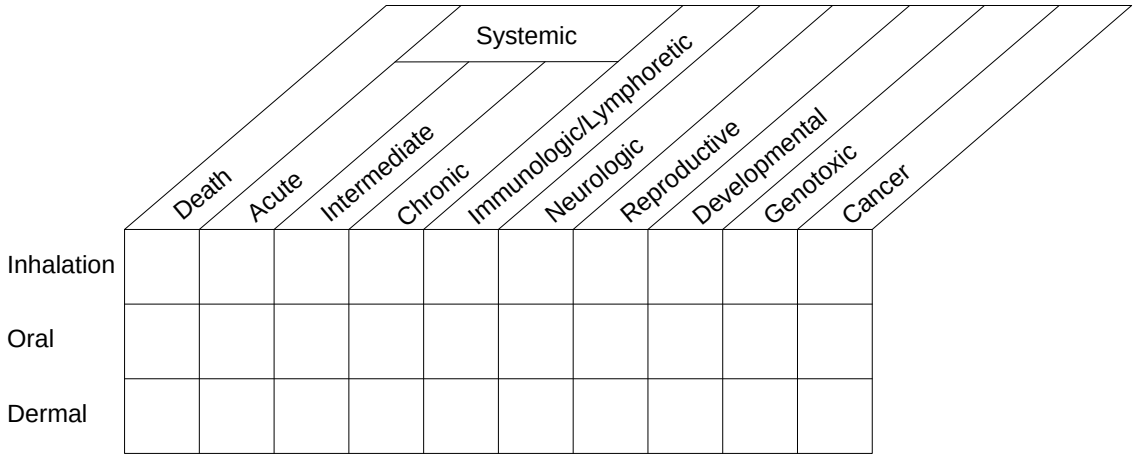
Human



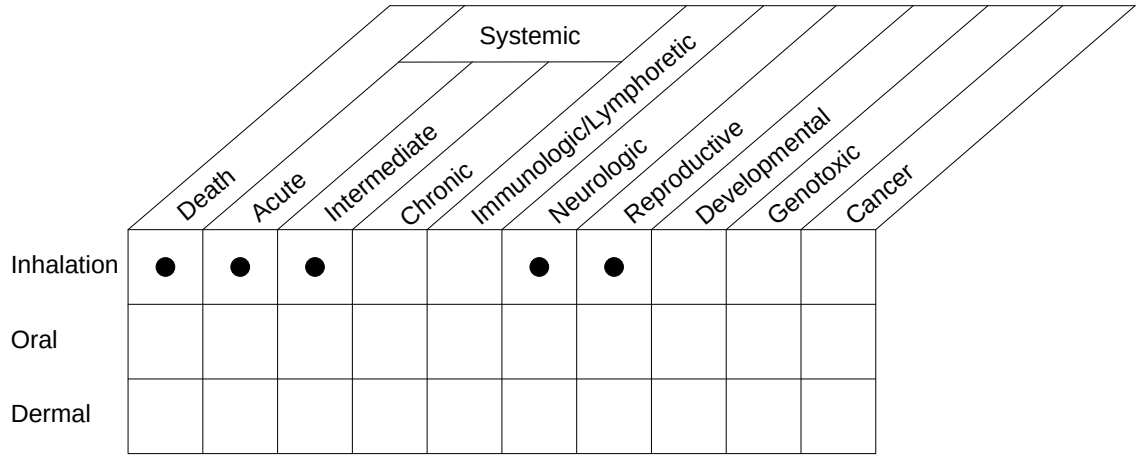
Animal

● Existing Studies

Figure 3-6. Existing Information on Health Effects of Carbonyl Sulfide



Human



Animal

● Existing Studies

al. 1989; Deng and Chang 1987; Freireich 1946; Hagley and South; Knight and Presnell 2005; Maebashi et al. 2011; Morse et al. 1981; Osbern and Crapo 1981; Parra et al. 1991; Policastro and Otten 2007; Reedy et al. 2011; Yalamanachili and Smith 2008) 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 15–120 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; Fiedler et al. 2008). Pulmonary function tests were normal in workers exposed to up to 10 ppm hydrogen sulfide (Jappinen et al. 1990). Suggestive 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.

Carbonyl Sulfide. Death occurred following a single inhalation exposure in rats (DuPont 1981; Monsanto 1985a) or repeated inhalation exposures in rats (Morgan et al. 2004) and rabbits (Hugod 1981; Hugod and Astrup 1980; Kamstrup and Hugod 1979). Neurotoxicity (including overt signs of toxicity and histological alterations in the brain) was observed in rats exposed via inhalation once or up to 12 times (Herr et al. 2007; Monsanto 1985b; Morgan et al. 2004; Morrison et al. 2009; Sills et al. 2004). Although these studies identified NOAELs and LOAELs and established dose-response relationships, the database was not considered adequate for derivation of an acute-duration inhalation MRL for carbonyl sulfide because there are insufficient data to determine whether neurotoxicity is the most sensitive end point. Additionally, studies that include examination of major tissues and organs are needed to determine if there are other sensitive targets of toxicity.

Intermediate-Duration Exposure.

Hydrogen Sulfide. 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 studies) 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 of 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. Although using the Brenneman et al. (2000) study as the basis of an intermediate-duration inhalation MRL was considered, the human equivalent concentration (HEC) of the NOAEL (5 ppm) was similar to

LOAELs identified for respiratory effects in humans acutely exposed to hydrogen sulfide. Thus, the database was considered inadequate for derivation 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.

Carbonyl Sulfide. Studies examining the toxicity of inhaled carbonyl sulfide following intermediate-duration exposure consist of a study in rabbits examining ultrastructural changes in the vascular system and heart (Hugod and Astrup 1980, Hugod 1981), a study examining morphological changes in the lungs, heart, and aorta of rabbits (Kamstup and Hugod 1979), several studies examining neurological end points (Herr et al. 2007; Morgan et al. 2004; Sills et al. 2004), and a reproductive toxicity study in male rats (Monsanto 1987). The animal studies clearly identify the nervous system and possibly the male reproductive system as targets of carbonyl sulfide toxicity. However, the lack of data from studies examining other major tissues and organs does not allow for the determination of the most sensitive targets of toxicity. Thus, an intermediate-duration inhalation MRL for carbonyl sulfide cannot be determined at this time. No oral or dermal exposure studies were identified.

Chronic-Duration Exposure and Cancer.

Hydrogen Sulfide. Studies of workers (Ahlborg 1951; Hessel et al. 1997; Richardson 1995), residents living in areas with high geothermal activity (Bates et al. 1997, 2002), residents living near paper mills (Haahtela et al. 1992; Jaakkola et al. 1990 Martttila et al. 1994a, 1994b, 1995; Partti-Pellinen et al. 1996), residents living near swine operations (Kilburn 2012; Schinasi et al. 2011), or residents living in other areas with high levels of hydrogen sulfide (Campagna et al. 2004; Carlsen et al. 2012; Legator et al. 2001) have reported increases in the occurrence of respiratory effects including irritation and alterations in lung function. Most of these studies have the common limitations of poorly reported exposure levels (or lack of monitoring data) and concomitant exposure to other compounds including mercaptans, sulfur dioxide, ammonia, and particulate matter. 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). No studies have examined the chronic toxicity or carcinogenicity of hydrogen sulfide in laboratory animals.

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.

Carbonyl Sulfide. No human or animal studies have examined the chronic toxicity or carcinogenicity of carbonyl sulfide following inhalation, oral, or dermal exposure. Chronic-duration animal studies are needed to identify targets of toxicity, establish dose-response relationships, and to evaluate the carcinogenic potential of carbonyl sulfide.

Genotoxicity.

Hydrogen Sulfide. No mutagenicity was observed in Ames assays using *Salmonella typhimurium* strains TA97, TA98, and TA100 (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.

Carbonyl Sulfide. No genotoxicity studies were located for carbonyl sulfide. *In vitro* studies are needed to assess whether carbonyl sulfide is genotoxic.

Reproductive Toxicity.

Hydrogen Sulfide. 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 warrant 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.

Carbonyl Sulfide. Information on the reproductive toxicity of carbonyl sulfide is limited to a study in which male rats were exposed to inhaled carbonyl sulfide prior to mating with unexposed females (Monsanto 1987). The study reported a decrease in pregnancy rate. Additional studies are needed to determine the cause of the decreased pregnancy rate and to evaluate whether carbonyl sulfide affects female reproduction.

Developmental Toxicity.

Hydrogen Sulfide. 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.

Carbonyl Sulfide. No studies evaluating the potential developmental toxicity of carbonyl sulfide were located. Developmental toxicity studies are needed to assess whether the developing organism is a sensitive target; these studies should include neurodevelopmental toxicity testing since neurotoxicity is a sensitive end point in adults.

Immunotoxicity.

Hydrogen Sulfide. Immunological effects infrequently observed after human hydrogen sulfide exposure appear to result from infection due to the aspiration or ingestion of manure or gastric contents (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.

Carbonyl Sulfide. No studies evaluating the potential immunotoxicity of carbonyl sulfide were located. Studies are needed to assess whether the immune system is a target of carbonyl sulfide toxicity.

Neurotoxicity.

Hydrogen Sulfide. 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 anecdotal 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.

Carbonyl Sulfide. Several acute- and intermediate-duration studies have evaluated the neurotoxicity of carbonyl sulfide in rats. The effects ranged from severe signs of neurotoxicity (including ataxia and hypothermia) and necrosis and neuronal loss in the parietal cortex, thalamus, and other midbrain structures to impaired performance on neurophysiological tests and motor function tests (Herr et al. 2007; Monsanto 1985b; Morgan et al. 2004; Morrison et al. 2009; Sills et al. 2004). These studies have identified NOAEL and LOAEL values for neurotoxicity and the results demonstrate a steep dose-response curve. Additional studies in different species would be useful in evaluating the relevance of the neurological effects observed in rats to humans.

Epidemiological and Human Dosimetry Studies.

Hydrogen Sulfide. 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). Some chronic-duration epidemiological studies (Ahlborg 1951; Haahtela et al. 1992; Horton et al. 2009; Inserra et al. 2004; Jaakkola et al. 1990; Jappinen et al. 1990; Marttila et al. 1994b; 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. Other studies evaluating respiratory effects (Campagna et al. 2004; Carlsen et al. 2012; Dongo et al. 2012; Kilburn 2012; Kilburn et al. 2010; Legator et al. 2001; Marttila et al. 1994a, 1995; Partti-Pellinen et al. 1996; Schinasi et al. 2011) or neurological effects (Bates et al. 1998; Farahat and Kishk 2010; Kilburn 1997; Legator et al. 2001) have not measured hydrogen sulfide levels. Epidemiology studies examining the potential effects of chronic inhalation exposure to various hydrogen sulfide concentrations are needed. Additionally, studies are needed that control for exposure to other contaminants such as methyl mercaptan, methyl sulfides, sulfur dioxide, and particulate matter. There are known populations that have unusually high exposure to hydrogen sulfide.

Carbonyl Sulfide. No human studies examining the potential toxicity of carbonyl sulfide in humans were identified. Studies are needed in populations exposed to carbonyl sulfide to evaluate potential targets of toxicity. Because the animal studies suggest that the nervous system is a sensitive target, epidemiology studies should include neurobehavioral testing.

Biomarkers of Exposure and Effect.

Exposure

Hydrogen Sulfide. 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.

Carbonyl Sulfide. There are no studies examining biomarkers of exposure to carbonyl sulfide, and such studies are needed.

Effect

Hydrogen Sulfide. 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.

Carbonyl Sulfide. No studies examining specific biomarkers of effect were identified for carbonyl sulfide.

Absorption, Distribution, Metabolism, and Excretion.

Hydrogen Sulfide. 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 may be 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.

Carbonyl Sulfide. There are very limited data on the toxicokinetics of carbonyl sulfide consisting of two studies that focused on its metabolism by carbonic anhydrase and the mixed function oxidase enzyme system (Chengelis and Neal 1979, 1980). More studies are needed evaluating the absorption, distribution, metabolism, and excretion of carbonyl sulfide.

Comparative Toxicokinetics.

Hydrogen Sulfide. 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.

Carbonyl Sulfide. There are currently insufficient data to characterize the toxicokinetics of carbonyl sulfide in any species; these data are needed for comparing the toxicokinetics across species.

Methods for Reducing Toxic Effects.

Hydrogen Sulfide. 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). Several case reports discussed the beneficial use of hyperbaric oxygen treatment (Asif and Exline 2012; Belley et al. 2005; Lindenmann et al. 2010); however, a rat study found that it decreased cytochrome c oxidase levels but did not affect the partial pressure of oxygen (Wu et al. 2011).

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 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.

Carbonyl Sulfide. No studies have examined methods for reducing the toxic effects of carbonyl sulfide. The available data are insufficient to characterize the toxicity of carbonyl sulfide. There is a potential for human exposure to carbonyl sulfide and studies designed to evaluate methods for reducing toxic effects should be done after the critical targets of toxicity and modes of action have been identified.

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.

Hydrogen Sulfide. 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). However, 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.

Carbonyl Sulfide. No studies were identified that could evaluate children's susceptibility to carbonyl sulfide. Studies in adult rats identify the nervous system as a sensitive target. Thus, future studies

examining children should evaluate neurological end points to evaluate whether they are more sensitive than adults.

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

NIEHS is sponsoring a study conducted by Michael Bates, University of California at Berkeley, to examine the chronic toxicity of hydrogen sulfide. The study will examine 1,800 adults living in Rotorua, New Zealand with high, medium, or low exposures to hydrogen sulfide from geothermal fields. The subjects will undergo tests to evaluate neurobehavioral function, peripheral nerve function, lung function, potential cataract formation, and color vision impairment.

The National Institute of Neurological Disorders and Stroke (NINDS) is sponsoring a study conducted by Gerry Boss, University of California at San Diego, to evaluate whether cobinamide (the pentultimate precursor in cobalamin [vitamin B12]), can be used as an antidote for hydrogen sulfide toxicity. In another NINDS-sponsored study, Philippe Haouzi, Pennsylvania State University, will examine the effectiveness of powdered methemoglobin and vitamin B12 (hydroxocobalamin) as an antidote in potentially lethal exposures to hydrogen sulfide.

No ongoing studies on carbonyl sulfide were identified.

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identities of hydrogen sulfide and carbonyl sulfide is located in Table 4-1. This information includes synonyms, chemical formula and structure, and identification numbers.

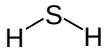
4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of hydrogen sulfide and carbonyl sulfide is located in Table 4-2.

Hydrogen Sulfide. Hydrogen sulfide is a heavier-than-air, colorless gas with a sweetish taste and characteristic odor of rotten eggs (HSDB 2013). The odor threshold for hydrogen sulfide is variable and various ranges have been reported. Ruth (1986) reviewed odor thresholds of several hundred chemicals (including hydrogen sulfide) from the industrial hygiene literature and other compilations of odor threshold data; an odor threshold range of 0.0005–0.010 ppm was reported. Guidotti (1994) reported an odor threshold range of 0.01–0.3 ppm. Since high concentrations of hydrogen sulfide (150–200 ppm) can paralyze the olfactory nerve, odor may not be a reliable indicator of the presence of this gas (Beauchamp et al. 1984).

Carbonyl Sulfide. Carbonyl sulfide is also a colorless gas with a typical sulfide odor, except when it is free from impurities (EPA 1994c; Lewis 2007). An odor threshold of 135 $\mu g/m^3$ (0.055 ppm) has been reported (Texas Commission on Environmental Quality 2008).

Table 4-1. Chemical Identity of Hydrogen Sulfide and Carbonyl Sulfide

Characteristic	Hydrogen sulfide[a]	Carbonyl sulfide[b]
Synonyms/trade names	Hydrosulfuric acid; hydrogen sulphide; stink damp; sewer gas; sulfur hydride; dihydrogen monosulfide; dihydrogen sulfide; sulfureted hydrogen; hydrogen sulfuric acid; acide sulfhydrique [French]; acide sulphhydrique; hydrogen sulfure [French]; hydrogene sulfure [French]; idrogeno solforato [Italian]; schwefelwasserstoff [German]; siarkowodor [Polish]; zwavelwaterstof [Dutch]	Carbon monoxide monosulfide; carbon oxide sulfide; carbon oxysulfide; oxycarbon sulfide; carbon oxide sulfide (9CI); carbon oxide sulfide (COS); carbonyl sulphide
Chemical formula	H_2S	COS
Chemical structure		
Identification numbers:		
CAS registry	7783-06-4	463-58-1
NIOSH/RTECS	MX1225000[c]	No data
EPA hazardous waste	U135	D003
DOT/UN/NA/IMCO shipping	UN1053; IMO 2.3	UN2204; IMO 2.3
HSDB	576	6127
EINECS	231-977-3	207-340-0
NCI	No data	No data

[a]All information obtained from HSDB 2013 and ChemID 2013 except where noted.
[b]All information obtained from HSDB 2007 and ChemID 2013.
[c]NIOSH 2011

CAS = Chemical Abstract Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EINECS = European Inventory of Existing Commercial Substances; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Identity of Hydrogen Sulfide and Carbonyl Sulfide

Property	Hydrogen sulfide	Carbonyl sulfide
Molecular weight	34.081[a]	60.075[b]
Color	Colorless[a]	Colorless[c]
Taste	Sweetish taste[a]	
Physical state	Gas[a]	Gas[c]
Melting point	-85.49°C[a]	-138.8°C[c]
Boiling point	-60.33°C[a]	-50.2°C[c]
Density in Air	1.189 (air=1.00)[c]	2.1 (air=1.00)[c]
Density at 0°C, 760 mmHg	1.5392 g/L[a]	
Odor	Strong odor of rotten eggs; offensive odor[a]	Typical sulfide odor except when pure[c]; odorless when pure, sulfur odor when it contains impurities[d]
Odor threshold:		
Water	0.000029 ppm[e]	
Air	0.0005–0.3 ppm[f,g]	135 µg/m^3[h]
Solubility:		
Water	3.98 g/L at 20°C[a]; 5.3 g/L at 10°C, 4.1 g/L at 20°C, 3.2 g/L at 30°C[i]	1.22 g/L at 25°C[b]
Other solvent(s)	Soluble in glycerol, gasoline, kerosene, carbon disulfide, crude oil; certain polar organic solvents, notably methanol, acetone, propylene carbonate, sulfolane, tributyl phosphate, various glycols, and glycol ethers[a]	Soluble in alcohol[c]; very soluble in potassium hydroxide, carbon disulfide[i]; soluble in toluene[b]
Partition coefficients:		
Log K_{ow}	Not applicable	
Log K_{oc}	Not applicable	
Vapor pressure at 25°C	13,600 mmHg at 20°C[a]	9412 mmHg[j]
pK_a (1)	7.04[a]	
pK_a (2)	11.96[a]	
Henry's law constant:		
at 20°C	468 atm/mole fraction[j]	
at 25°C	0.0098 atm-m^3/mole[a]	
at 30°C	600 atm/mole fraction[j]	
at 40°C	729 atm/mole fraction[j]	

Table 4-2. Physical and Chemical Identity of Hydrogen Sulfide and Carbonyl Sulfide

Property	Hydrogen sulfide	Carbonyl sulfide
Autoignition temperature	500°F (260°C)[c]	
Incompatibilities		Oxidizing agents (i.e., perchlorates, peroxides, permanganates, chlorates, nitrates, chlorine, bromine, fluorine); may react with water and moist air[k]
Conversion factors	1 ppm=1.40 mg/m^3[l]	1 mg/m^3=0.41 ppm[m]
Explosive limits	Upper, 46%; lower, 4.3% (by volume in air)[a]	Upper, 28.5%; lower, 12%[c]

[a]HSDB 2013
[b]HSDB 2007
[c]Lewis 2007
[d]EPA 1994c
[e]Amoore and Hautala 1983
[f]Ruth 1986
[g]Guidotti 1994
[h]Texas Commission on Environmental Quality 2008
[i]O'Neil et al. 2001
[j]Daubert and Danner 1989
[k]NJDEP 2009
[l]Al-Haddad et al. 1989
[m]EPA 1994a

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Hydrogen Sulfide. Hydrogen sulfide is produced in technical (98.5%) and purified (99.5% minimum) grades (Lewis 2007). It is commercially available by two typical approaches: recovery from gas mixtures and chemical means. Natural gas and gases associated with crude oil contain varying amounts of hydrogen sulfide from trace amounts to 70–80% (Pouliquen et al. 1989). Recovery of hydrogen sulfide from natural gas, manufactured gas operations, or as a byproduct of petroleum refining is the main non-natural source of hydrogen sulfide (Beauchamp et al. 1984; Lewis 2007). These recovery processes can be categorized into several methods, including chemical and physical absorption, dry oxidation to form sulfur or oxides (Clause process), and liquid oxidation to form oxides (Ferrox process) (Beauchamp et al. 1984).

Hydrogen sulfide production by chemical reaction can involve reacting sulfur vapor either with a hydrocarbon (Pouliquen et al. 1989) or with hydrogen gas (H_2) at a specific temperature and pressure (Lewis 2007). It can also be produced by the hydrogen reduction or acid decomposition of a sulfide (Pouliquen et al. 1989), such as the reaction of dilute sulfuric acid on a sulfide (i.e., iron sulfide) (Lewis 2007). Another method of hydrogen sulfide production, which accounts for >90% of the sulfur in crude oil, is hydrodesulfurization, in which gas-oil and coke distillate fractions are passed through a fixed-bed catalyst in the presence of hydrogen. Approximately 80–90% of the sulfur-containing compounds (mostly acyclic and cyclic sulfides) are converted into hydrogen sulfide by this process (Beauchamp et al. 1984; Weil and Sandler 1997).

Table 5-1 lists the facilities in each state that manufacture, process, or use hydrogen sulfide as well as the volume ranges that are stored on-site. There are 486 facilities that produce or process hydrogen sulfide in the United States (TRI12 2013).

Carbonyl Sulfide. Carbonyl sulfide is produced as 97.5% minimum purity grade (HSDB 2007). It can be made from hydrolysis of ammonium or potassium thiocyanate (Lewis 2007) using dilute sulfuric acid (HSDB 2007), as a byproduct of carbon disulfide production (EPA 1994c, 1994d; HSDB 2007), by the reaction of carbon monoxide with sulfur, by the reduction of sulfur dioxide with carbon, or by the reaction of phosgene and cadmium sulfide (HSDB 2007). It is also produced as an impurity in natural gas and refinery gases as well as from the combustion of sulfur-containing fuels. Carbonyl sulfide can result from the pyrolysis of carbonaceous fuels with oxygen, steam, and sulfur compounds (HSDB 2007).

Table 5-1. Facilities that Produce, Process, or Use Hydrogen Sulfide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10,000	99,999	1, 10, 12, 13
AL	31	0	999,999	1, 2, 3, 5, 6, 12, 13, 14
AR	12	0	999,999	1, 5, 6, 12, 13, 14
AZ	2	0	0	0
CA	28	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 13, 14
CO	5	0	999,999	1, 5, 13, 14
DE	4	0	499,999,999	1, 2, 5, 6, 7, 12
FL	13	0	9,999	1, 5, 12, 14
GA	20	0	99,999	1, 2, 3, 5, 6, 12, 13
HI	2	1,000	99,999	1, 3, 5, 12, 14
IA	4	0	9,999	1, 5
ID	4	100	9,999,999	1, 5, 14
IL	17	0	999,999,999	1, 2, 3, 5, 6, 7, 9, 12, 13, 14
IN	11	0	999,999	1, 5, 7, 13, 14
KS	8	0	999,999	1, 5, 6, 9, 13, 14
KY	7	0	999,999	1, 2, 5, 6, 12, 13, 14
LA	42	0	49,999,999	1, 2, 3, 5, 6, 7, 9, 10, 12, 13, 14
MA	1	0	0	0
MD	2	0	9,999	1, 5, 13
ME	6	0	999,999	1, 5
MI	5	0	999,999	1, 2, 3, 4, 5, 12, 13
MN	8	100	49,999,999	1, 5, 13, 14
MO	6	0	9,999,999	1, 2, 3, 4, 5, 6, 9, 11, 14
MS	11	100	9,999,999	1, 2, 5, 6, 12, 13, 14
MT	5	0	99,999	1, 2, 3, 4, 5, 6, 8, 9, 13, 14
NC	10	0	9,999,999	1, 5, 13
ND	5	0	9,999,999	1, 5, 9, 13, 14
NE	6	100	9,999	1, 5
NH	1	100	999	12
NJ	5	0	999,999	1, 2, 5, 6, 13, 14
NM	5	0	999,999	1, 5, 6, 13, 14
NV	1	0	0	0
NY	7	0	99,999	1, 5, 9, 12, 13
OH	21	0	49,999,999	1, 2, 3, 4, 5, 6, 9, 12, 13, 14
OK	12	0	99,999	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
OR	5	100	99,999	1, 5
PA	13	0	99,999,999	1, 2, 3, 5, 7, 10, 13, 14
PR	1	1,000,000	9,999,999	1, 5
SC	9	100	99,999	1, 5, 12, 13, 14
SD	1	10,000	99,999	1, 5

Table 5-1. Facilities that Produce, Process, or Use Hydrogen Sulfide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	8	0	9,999	1, 5, 13, 14
TX	75	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 11, 12, 13, 14
UT	3	1,000	9,999,999	1, 2, 3, 5, 6, 10, 12, 13, 14
VA	8	0	99,999	1, 5, 6, 13, 14
VI	1	100,000	999,999	2, 5, 14
WA	14	100	9,999,999	1, 2, 3, 5, 6, 7, 12, 13, 14
WI	13	0	99,999	1, 5, 6, 12, 13, 14
WV	2	1,000	99,999	1, 5, 6, 13
WY	4	1,000	99,999	1, 5, 7, 12, 13, 14
AK	1	10,000	99,999	1, 10, 12, 13

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI12 2013 (Data are from 2012)

Carbonyl sulfide can also be found in tobacco smoke as well as emissions from diesel engines and the coal gasification process (NJDEP 2009). Additionally, carbonyl sulfide is found in numerous natural sources, including volcanic gases, petroleum crude oil, sulfurous waters, salt marshes, and soils (EPA 1994c; GoodGuide 2011). It can also emanate from deciduous and coniferous trees (GoodGuide 2011).

Table 5-2 lists the facilities in each state that manufacture, process, or use carbonyl sulfide as well as the volume ranges that are stored on-site. There are 134 facilities that produce or process carbonyl sulfide in the United States (TRI11 2013).

5.2 IMPORT/EXPORT

No data on import or export volumes for hydrogen sulfide or carbonyl sulfide are available.

5.3 USE

Hydrogen Sulfide. Hydrogen sulfide has a variety of industrial uses. Its major use is in the production of elemental sulfur and sulfuric acid. Sulfur recovered from the treatment of sour gas in 1986 accounted for 14 million tons, or 25% of total world sulfur production. In 1995, the production of sulfuric acid was estimated to consume $1.1x10^5$ metric tons of hydrogen sulfide. Hydrogen sulfide is used to prepare inorganic sulfides (such as sodium sulfide and sodium hydrosulfide) which are used in the manufacture of dyes, rubber chemicals, pesticides, polymers, plastic additives, leather, and pharmaceuticals. It is also used in the manufacture of metal sulfides and thioorganic compounds and is an intermediate for sulfuric acid and elemental sulfur production. Hydrogen sulfide is used in the purification of nickel, manganese, hydrochloric acid, and sulfuric acid; in catalyst activation and poisoning; in the treatment of metallic surfaces; and as a source of hydrogen. It is used in metallurgy, in the production of heavy water for the nuclear industry, and as an analytical reagent. In extreme pressure lubricants and cutting oils, hydrogen sulfide is used as an additive. Hydrogen sulfide is also used as an agricultural disinfectant. It is not registered as a pesticide in the United States (Beauchamp et al. 1984; Bingham et al. 2001; HSDB 2013; Lewis 2007; Sittig 2002; Weil and Sandler 1997).

Carbonyl Sulfide. Carbonyl sulfide has few commercial uses; it is primarily used in small scale chemical syntheses (HSDB 2007). Carbonyl sulfide is a chemical intermediate in the manufacture of thiocarbamate herbicides (EPA 1994d; HSDB 2007). It can be used in the synthesis of aliphatic polyureas as well as for the production of alkyl carbonates and other organic compounds (GoodGuide

Table 5-2. Facilities that Produce, Process, or Use Carbonyl Sulfide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	0	99	1, 5
AL	3	0	999,999	1, 5, 6, 12, 14
AR	1	1,000	9,999	1, 3, 5, 6
CA	13	0	9,999,999	1, 2, 3, 5, 6, 13, 14
DE	2	10,000	99,999	1, 3, 5, 6
HI	1	0	99	1, 13
ID	1	0	99	1, 5
IL	6	0	999,999	1, 3, 4, 5, 6, 13, 14
IN	7	0	99,999	1, 5, 12, 13
KS	6	0	999	1, 5, 14
KY	3	100	99,999	1, 5, 14
LA	19	0	9,999,999	1, 3, 5, 6, 12, 13, 14
MI	1	100	999	1, 5
MN	3	100	999,999	1, 2, 3, 5, 6, 13
MS	3	100	999,999	1, 5, 6, 12
MT	3	0	999	1, 5, 13, 14
ND	1	0	99	1, 5
NM	1	0	99	1, 5
NV	1	0	99	1, 5
NY	2	0	99	1, 5
OH	9	0	999,999	1, 3, 5, 12, 13
OK	5	0	9,999	1, 5, 12, 13, 14
PA	1	0	99	1, 5, 13
SC	1	0	99	1, 5
TN	3	0	9,999	1, 5, 6, 13, 14
TX	24	0	9,999,999	1, 2, 3, 5, 6, 12, 13, 14
UT	3	0	999	1, 5
VI	1	10,000	99,999	1, 5
WA	6	0	9,999	1, 5, 13
WI	1	1,000	9,999	1, 5
WY	2	0	9,999	1, 5

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacturing Aid
12. Ancillary/Other Uses
13. Manufacturing Impurity
14. Process Impurity

Source: TRI11 2013 (Data are from 2011)

2011; HSDB 2007). It may also be used in the production of semiconductors (Chase et al. 2010). Refinery and fuel gases can contain carbonyl sulfide as an impurity. Combustion of sulfur-containing fuels can also result in the formation of carbonyl sulfide (EPA 1994d). More recently, carbonyl sulfide has been used as a highly effective grain fumigant in place of the ozone-depleting methyl bromide (HSDB 2007; NJDEP 2009; Wright 2000). In the same capacity, it can also be used in conjunction with phosphine gas to reduce insect resistance (HSDB 2007).

5.4 DISPOSAL

Hydrogen Sulfide. Hydrogen sulfide is designated as a hazardous substance under Section 311(b) of the Clean Water Act (EPA 2009d). Disposal of wastes containing hydrogen sulfide is controlled by a number of federal regulations (see Chapter 8). The EPA-assigned hazardous waste number for hydrogen sulfide is U135 (EPA 2012b). Generators of waste exceeding 100 pounds/month containing hydrogen sulfide must conform to the EPA regulations for the storage, transportation, treatment, and disposal of waste (EPA 2012f). Additional information concerning the accidental release of hydrogen sulfide and its reporting requirements is found in Chapter 8.

Carbonyl Sulfide. Carbonyl sulfide has been cited by the Department of Transportation (DOT), Department of Environmental Protection (DEP), Integrated Risk Information System (IRIS), National Fire Protection Association (NFPA), and EPA and is therefore on the New Jersey Right to Know Hazardous Substance List (NJDEP 2009). When disposing of carbonyl sulfide, care should be taken to avoid contamination of the surrounding environment (National Iranian Gas Company 2012). Carbonyl sulfide has an EPA hazardous waste number of D003, and therefore, those generating waste exceeding 100 kg/month (like hydrogen sulfide) must comply with EPA requirements (HSDB 2007).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Hydrogen sulfide has been found in at least 35 of the 1,689 waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) and carbonyl sulfide was detected in at least 3 of the 1,689 waste sites (HazDat 2007). However, the number of sites evaluated for these substances is not known and hydrogen sulfide and carbonyl sulfide are ubiquitous in the atmosphere. The frequency of these sites can be seen in Figures 6-1 and 6-2.

Carbonyl sulfide and hydrogen sulfide are principal components in the natural sulfur cycle (HSDB 2007, 2013). Bacteria, fungi, and actinomycetes (a fungus-like bacteria) release hydrogen sulfide during the decomposition of sulfur containing proteins and by the direct reduction of sulfate (SO_4^{2-}). Hydrogen sulfide is also emitted from volcanoes, stagnant or polluted waters, and manure or coal pits with low oxygen content (HSDB 2013). The majority of carbonyl sulfide that enters the environment is released to air and it is very abundant in the troposphere (Conrad and Meuser 2000; EPA 1994c, 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; Simmons et al. 2012; Stimler et al. 2010). It enters the atmosphere from both natural and anthropogenic sources (EPA 1994c, 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010). Carbonyl sulfide is released from wetlands, salt marshes, soil, oceans, deciduous and coniferous trees, and volcanic gases (Blake et al. 2004; EPA 1994c, 1994d; Meinrat et al. 1992; Rasmussen et al. 1982a, 1982b; Stimler et al. 2010). 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 (ASTM International 2012; Blake et al. 2004; EPA 1994c, 1994d; PERC 2001). Natural sources of carbonyl sulfide and hydrogen sulfide are significantly greater than anthropogenic emissions.

Carbonyl sulfide can be removed from the atmosphere by terrestrial vegetation, soils, photolysis, and reaction with hydroxyl and oxygen radicals (Blake et al. 2004; EPA 1994d; GoodGuide 2011; National Iranian Gas Company 2012; Stimler et al. 2010). Decomposition of carbonyl sulfide by moisture results in the formation of carbon dioxide and hydrogen sulfide. Hydrogen sulfide is consumed by bacteria found in soil and water that oxidize hydrogen sulfide to elemental sulfur. Photosynthetic bacteria can

Figure 6-1. Frequency of NPL Sites with Hydrogen Sulfide Contamination

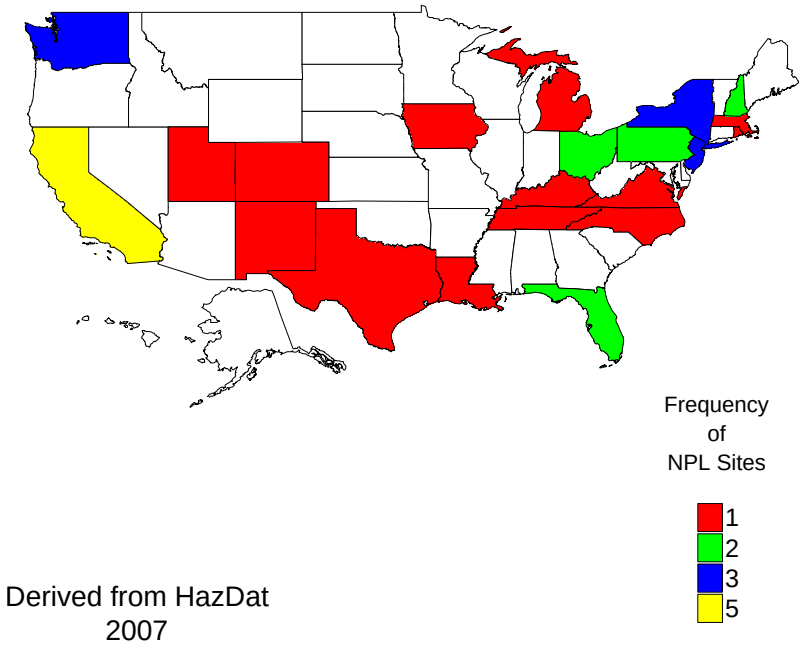
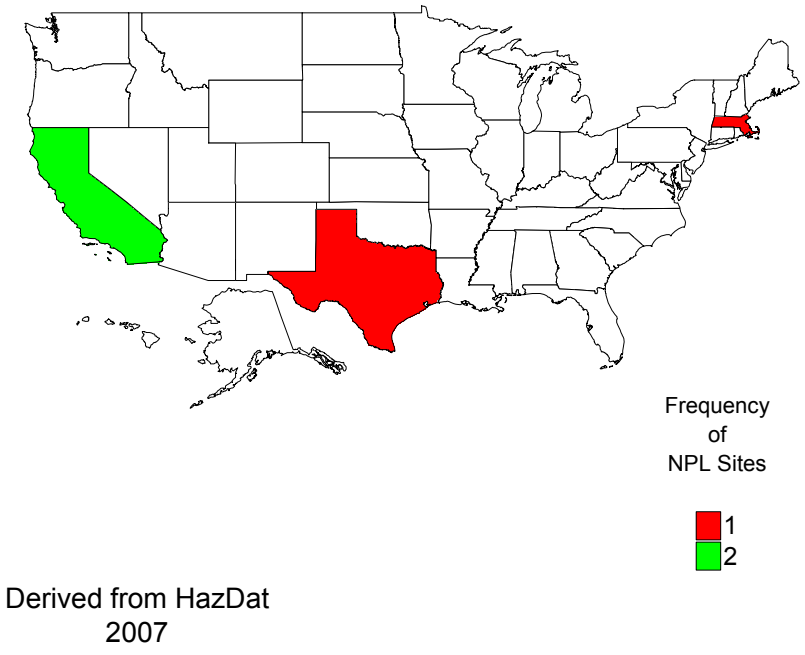


Figure 6-2. Frequency of NPL Sites with Carbonyl Sulfide Contamination



oxidize hydrogen sulfide to sulfur and sulfate in the presence of light and the absence of oxygen (EPA 1993; WHO 1981).

Degradation of hydrogen sulfide in the atmosphere can occur through oxidation by oxygen (O_2) and ozone (O_3) to yield sulfur dioxide (SO_2), and ultimately, sulfate compounds. Sulfur dioxide and sulfates are eventually removed from the atmosphere through absorption by plants and soils or through precipitation (Hill 1973). Hydrogen sulfide in air can also react with photochemically generated hydroxyl radicals. The effective lifetimes for hydrogen sulfide based on summer daytime and yearly average hydroxyl radical concentrations have been estimated to be 0.23 and 2.3 days, respectively, based on a measured rate constant of $4.8x10^{-12}$ cm^3/molecule second (Cox 1975). Lifetimes in air ranging from approximately 1 day in the summer to 42 days in the winter have been estimated for hydrogen sulfide (Bottenheim and Strausz 1980). Hydrogen sulfide is not expected to be decomposed by direct absorption of ultraviolet radiation, and its reaction with ozone is not expected to be a significant environmental fate (Cox 1975).

Hydrogen sulfide oxidation by O_2 may readily occur in surface waters (Millero et al. 1987, 1989). Hydrogen sulfide is readily soluble in water. In aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-), and the second yields sulfide ion (S^{2-}), with pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). At a pH of 7.0, the ratio of the concentration of aqueous hydrogen sulfide to bisulfate ion is approximately 1-to-1. As the pH increases above 7.0, the ratio of the concentration of bisulfide ion to aqueous hydrogen sulfide increases. Only above pH 12 will the concentration of sulfide ion become significant (>50%). Hydrogen sulfide has been shown to sorb to various soils (Cihacek and Bremner 1993; Smith et al. 1973). Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur, and its half-time in these environments usually ranges from 1 hour to several hours (Jørgensen 1982). Because it is a gas under ambient conditions, bioconcentration and food chain biomagnification are unlikely (HSDB 2013).

While carbonyl sulfide is relatively inert in the troposphere, with a reported lifetime ranging from 2 to 10 years (Blake et al. 2004; EPA 1994d; GoodGuide 2011; Liu et al. 2007; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010), it is transported to the stratosphere where it undergoes photolysis and reaction with oxygen and photochemically-produced hydroxyl radicals (EPA 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010). It may contribute to ozone depletion (Conrad and Meuser 2000; Liu et al. 2007; Meinrat et al. 1992; Simmons et al. 2012).

Carbonyl sulfide can enter water and soil through atmospheric deposition. In water, carbonyl sulfide reacts with the water to form carbon dioxide and hydrogen sulfide. It is expected to rapidly volatilize to air. Carbonyl sulfide does not bind to soils and may be transported to groundwater (EPA 1994c; Meinrat et al. 1992; National Iranian Gas Company 2012). While soils could potentially be both a sink and a source to the atmosphere, recent data indicate that soils are primarily a sink for atmospheric carbonyl sulfide (Conrad and Meuser 2000; Kato et al. 2008; Liu et al. 2007, 2010; Simmons et al. 2012; Stimler et al. 2010). Carbonyl sulfide has been found to biodegrade in soils (Kato et al. 2008). It is not expected to bioconcentrate in aquatic organisms (EPA 1994c, 1994d; National Iranian Gas Company 2012).

Exposure of the general population to hydrogen sulfide and carbonyl sulfide is primarily through inhalation of ambient air, as these substances are ubiquitous in the atmosphere. Occupational exposure to carbonyl sulfide is primarily a result of its production and use as a chemical intermediate (EPA 1994d) and its production as a byproduct in petroleum refining and coal distillation (GoodGuide 2011). Occupational exposure to hydrogen sulfide occurs at facilities where it is produced, used, or generated such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacturing plants, sulfur production plants, iron smelters, food processing plants, manure treatment facilities, landfills, textile plants, waste water treatment facilities, and tanneries (Chénard et al. 2003; Devai and DeLaune 1999; Lehman 1996; Rimatori et al. 1996; Svendsen 2001).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in the following Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and

if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

There are no TRI release facilities data for hydrogen sulfide.

6.2.1 Air

Estimated releases of 13.8 million pounds (~6,261 metric tons) of carbonyl sulfide to the atmosphere from 134 domestic manufacturing and processing facilities in 2011, accounted for about 99% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). These releases are summarized in Table 6-1.

There is no information on releases of hydrogen sulfide to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

Hydrogen Sulfide. Hydrogen sulfide is produced naturally and as a result of human activity. Natural sources, such as swamps, bogs, and volcanoes, account for about 90% of the total amount of hydrogen sulfide in the atmosphere (EPA 1993). Annually, 100–324 million tons of hydrogen sulfide are released from natural sources with half from volcanoes, flooded ground, or hydrogeological sources, and the other half from the oceans (Pouliquen et al. 1989). Massive release of hydrogen sulfide to the ocean surface and atmosphere could occur during intervals of ocean anoxia (Kump et al. 2005). Nearshore hydrogen sulfide eruptions occur in the Atlantic Ocean along the central coast of Nambia and have been observed to affect areas of ocean surface of >20,000 km^2 (Weeks et al. 2004). Many petroleum deposits and natural gas wells also contain hydrogen sulfide ("sour-gas wells") and become sources of atmospheric hydrogen sulfide release when developed (Layton and Cederwall 1986; Leahey and Schroeder 1986). Hydrogen sulfide is emitted by some plant species as a byproduct of sulfite metabolism (Takemoto et al. 1986; Wilson et al. 1978). Emission rates of various biogenic sulfur gases (including hydrogen sulfide) from the exposed soils of five wetland plant communities in Florida were measured during April, May, and October 1985 and January 1986. Emission rates for hydrogen sulfide varied from 0.1–1.0 to 8.3–152 μg sulfur/m^2/hour from a spike grass site in the Everglades National Park in January 1986 and a sawgrass site at Merritt Island National Wildlife Refuge in April 1985, respectively (Cooper et al. 1987). Hydrogen sulfide was identified in the volatile emissions of leaf litter of poplar trees (*Populus balsamifera*) (Isidorov and Jdanova 2002). Estimates of the terrestrial emission rates of hydrogen sulfide

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Carbonyl Sulfide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	460	0	0	0	0	460	0	460
AL	3	132,386	0	0	0	0	132,386	0	132,386
AR	1	1,045	0	0	0	0	1,045	0	1,045
CA	13	38,185	0	0	0	0	38,185	0	38,185
DE	2	198,079	0	0	0	0	198,079	0	198,079
HI	1	1,000	0	0	0	0	1,000	0	1,000
ID	1	6,403	0	0	0	0	6,403	0	6,403
IL	6	44,855	0	0	0	0	44,855	0	44,855
IN	7	1,178,233	0	0	0	0	1,178,233	0	1,178,233
KS	6	105,819	0	0	0	0	105,819	0	105,819
KY	3	766,590	0	0	0	0	766,590	0	766,590
LA	19	210,130	876	0	28	0	211,006	28	211,034
MI	1	0	0	0	0	0	0	0	0
MN	3	5,410	0	0	0	0	5,410	0	5,410
MS	3	888,793	0	0	0	0	888,793	0	888,793
MT	3	286	0	0	0	0	286	0	286
ND	1	12,770	0	0	0	0	12,770	0	12,770
NM	1	0	0	0	0	0	0	0	0
NV	1	203	0	0	0	0	203	0	203
NY	2	672,800	0	0	0	0	672,800	0	672,800
OH	8	5,230,398	0	0	0	0	5,230,398	0	5,230,398
OK	5	1,278	0	0	0	0	1,278	0	1,278
PA	1	31	0	0	0	0	31	0	31
SC	1	900,000	0	0	0	0	900,000	0	900,000
TN	3	2,256,893	0	0	0	0	2,256,893	0	2,256,893
TX	24	200,600	0	0	0	0	200,600	0	200,600
UT	3	1,615	0	0	0	0	1,615	0	1,615
VI	1	13,962	0	0	0	0	13,962	0	13,962
WA	6	879,478	0	0	0	0	879,478	0	879,478
WI	1	1,016	0	0	0	0	1,016	0	1,016

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Carbonyl Sulfide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WY	2	7,301	0	0	0	0	7,301	0	7,301
Total	134	13,756,018	876	0	28	0	13,756,894	28	13,756,922

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI11 2013 (Data are from 2011)

range from 58 to 110 million tons of sulfur/year and estimates of the emission rates from oceans range from 30 to 170 million tons of sulfur/year (Hill 1973).

Facilities where hydrogen sulfide is produced, used, or generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacturing plants, sulfur production plants, iron smelters, food processing plants, manure treatment facilities, landfills, textile plants, waste water treatment facilities, and tanneries (ACGIH 1991; Beck et al. 1981; Chénard et al. 2003; Devai and DeLaune 1999; Grant and Schuman 1993; Lehman 1996; Rimatori et al. 1996; Sittig 2002; Svendsen 2001). Hydrogen sulfide is also used as an agricultural disinfectant, in the production of heavy water, and as an additive in lubricants and cutting oils (ACGIH 1991; Bingham et al. 2001; HSDB 2013; Sittig 2002; Weil and Sandler 1997). Hydrogen sulfide may also be encountered in various industrial processes including the manufacture of dyes and pigments, felt, artificial silk, farming; in brewing, glue making, and rubber vulcanization; and in lithography and photoengraving (Beck et al. 1981; Grant and Schuman 1993; Sittig 2002). Accidental release or improper disposal of materials resulting from these processes may result in hydrogen sulfide emissions. Ambient hydrogen sulfide concentrations in the air near landfills indicate that they are a source as well (HazDat 2007). Sulfides, including hydrogen sulfide, constitute up to 1% by volume of typical landfill gases (Agency for Toxic Substances and Disease Registry 2001). The Fresh Kills Landfill on Staten Island, New York has been estimated to release approximately 16 tons of hydrogen sulfide to the air annually (Agency for Toxic Substances and Disease Registry 2000). Facilities that treat manure may also release hydrogen sulfide to the air. Hydrogen sulfide emissions were measured from two anaerobic lagoons used for treating swine waste; the overall mean hydrogen sulfide release was 5.7 $\mu g/m^2$/second (Lim et al. 2003).

Carbonyl Sulfide. Section 112 of the Clean Air Act (CAA) lists carbonyl sulfide as one of 189 hazardous air pollutants (HAPs) known or suspected to cause cancer or other serious human health effects or ecosystem damage (EPA 2009d). EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from multiple sources including state and local environmental agencies, the TRI database, computer models for on-road and off-road emissions, and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Data downloaded from the 2008 NEI indicated that the total emission of carbonyl sulfide was approximately 25.5 million pounds, with the

biggest source arising from chemical manufacturing and oil and gas production (EPA 2013f). No data were available for hydrogen sulfide in the 2008 NEI.

The vast majority of carbonyl sulfide that enters the environment is released into the air (EPA 1994c, 1994d; National Iranian Gas Company 2012). Of the sulfur-containing gases, carbonyl sulfide is the most abundant in the troposphere (Conrad and Meuser 2000; Meinrat et al. 1992; Simmons et al. 2012; Stimler et al. 2010). Carbonyl sulfide is a gas that can enter the atmosphere from both natural and anthropogenic sources (EPA 1994c, 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010). Natural sources account for the atmospheric release of approximately 4 billion pounds of carbonyl sulfide each year (EPA 1994c). It is released naturally from wetlands and salt marshes, soil, both deciduous and coniferous trees, and volcanic gases (Blake et al. 2004; EPA 1994c, 1994d). Oceans contribute a significant amount of carbonyl sulfide to the atmosphere (Meinrat et al. 1992; Rasmussen et al. 1982a; Stimler et al. 2010). Yearly emissions of carbonyl sulfide from oceans have been quantified as approximately $8x10^{11}$ gm/year (0.8 Tg/year) (Rasmussen et al. 1982a) and 12.7 Gmol/year (0.41 Tg sulfur/year) (Meinrat et al. 1992).

The extraction of natural gas can result in the formation of carbonyl sulfide. When natural gas sources are saturated with water, hydrogen sulfide and carbon dioxide are formed (i.e., “sour gas”). These products undergo a hydrolysis reaction resulting in the formation of carbonyl sulfide and water. Using adsorbent materials for dehydration in this process is a significant factor in the creation of carbonyl sulfide (PERC 2001). Carbonyl sulfide is also found in the inlet gas to natural gas liquids recovery facilities, where it has a tendency to concentrate in the propane and propylene streams (ASTM International 2012; PERC 2001).

Blake et al. (2004) quantified the carbonyl sulfide emissions from various anthropogenic sources from different countries located in Asia. Ranges (and total emission) resulting from the combustion of various fuels were as follows (conversion factor is 1 Gg/year=1,000 metric tons/year): coal, 0.048–4.4 Gg/year (total emissions of 7.3 Gg/year); oil plants, 0.11–1.4 Gg/year (3.4 Gg/year); biofuel, 0.16–19.9 Gg/year (56.6 Gg/year); transport, 0.10–1.4 Gg/year (3.1 Gg/year); and biomass burning, 0.14–12.6 Gg/year (31.2 Gg/year). Emissions from industrial production ranged from 0.01 to 15.7 Gg/year (total emissions of 33.9 Gg/year, while landfills emissions were responsible for 0.0005–0.009 Gg/year (0.02 Gg/year). Agricultural sources included rice paddies, which had emissions ranging from 0.14 to 3.5 Gg/year (total emissions of 10.7 Gg/year), and animal feedlots, which had emissions ranging from 0.0002 to

0.006 Gg/year (total emissions of 0.01 Gg/year). The total anthropogenic emissions of carbonyl sulfide in Asia were determined to be 146 Gg/year (Blake et al. 2004).

6.2.2 Water

Estimated releases of 876 pounds (~0.40 metric tons) of carbonyl sulfide to surface water from 134 domestic manufacturing and processing facilities in 2011, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). These releases are summarized in Table 6-1.

There is no information on releases of hydrogen sulfide to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

Hydrogen Sulfide. Releases of hydrogen sulfide to water occur both naturally and as a result of human activity. Hydrogen sulfide released from aquatic plants or as a result of anaerobic chemical processes in swamps and bogs may dissolve in the water column or bind to clay or organic matter. Massive release of hydrogen sulfide to the ocean surface could occur during intervals of ocean anoxia (Kump et al. 2005).

Facilities where hydrogen sulfide is produced, used, or generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacturing plants, sulfur production plants, iron smelters, food processing plants, manure treatment facilities, landfills, textile plants, waste water treatment facilities, and tanneries (ACGIH 1991; Beck et al. 1981; Chénard et al. 2003; Devai and DeLaune 1999; Grant and Schuman 1993; Lehman 1996; Rimatori et al. 1996; Sittig 2002; Svendsen 2001). Hydrogen sulfide is also used as an agricultural disinfectant, in the production of heavy water, and as an additive in lubricants and cutting oils (ACGIH 1991; Bingham et al. 2001; HSDB 2013; Sittig 2002; Weil and Sandler 1997). Hydrogen sulfide may also be encountered in various industrial processes including the manufacture of dyes and pigments, felt, and artificial silk; in farming, brewing, glue making, and rubber vulcanization; and in lithography and photoengraving (Beck et al. 1981; Grant and Schuman 1993; Sittig 2002). Discharge liquids from these and other activities can release hydrogen sulfide to receiving waters (EPA 1993).

Carbonyl Sulfide. Carbonyl sulfide is a gas and is therefore primarily released to water through atmospheric deposition. When released to water, carbonyl sulfide will dissolve and may react with the water to form hydrogen sulfide (EPA 1994c). When in water, it is expected to quickly volatilize to air

(EPA 1994c; National Iranian Gas Company 2012). Oceans, in particular, are known to be a significant source of carbonyl sulfide to the atmosphere, with emissions calculated as approximately $8x10^{11}$ gm/year (800,000 metric tons/year) (Meinrat et al. 1992; Rasmussen et al. 1982a).

6.2.3 Soil

Estimated releases of 28 pounds (~0.01 metric tons) of carbonyl sulfide to soils from 134 domestic manufacturing and processing facilities in 2011, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI11 2013). These releases are summarized in Table 6-1.

There is no information on releases of hydrogen sulfide to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 1998a).

Hydrogen Sulfide. Hydrogen sulfide may enter the soil through deposition from the atmosphere, migration of mobilized pore water, or from leaks and spills associated with manufacture, transport, or storage. Hydrogen sulfide is readily soluble in water and would exist as bisulfide or sulfide ions. Hydrogen sulfide can also form insoluble sulfide salts with various metals (i.e., copper, zinc, nickel, and iron) that may be present in soils (Pouliquen et al. 1989).

Carbonyl Sulfide. Like hydrogen sulfide, carbonyl sulfide may enter soil through atmospheric deposition. It does not bind well to soils and may be transported to groundwater. Carbonyl sulfide is typically released to air from both moist and dry soils (EPA 1994c; National Iranian Gas Company 2012). There is some discrepancy, however, amongst the literature as to whether soil is a source or a sink of carbonyl sulfide (Simmons et al. 2012). Previous studies labeled soil as a source of carbonyl sulfide to the atmosphere, as noted by Liu et al. (2007) and Simmons et al. (2012). However, more recent sources indicate the converse, that soil is a significant sink of atmospheric carbonyl sulfide (Kato et al. 2008; Liu et al. 2007, 2010; Simmons et al. 2012; Stimler et al. 2010). In particular, oxic soils are known to be a carbonyl sulfide sink (Liu et al. 2007, 2010). There is evidence that indicates that soils may be both sources and sinks of carbonyl sulfide (Conrad and Meuser 2000).

Simmons et al. (2012) found that soils (both with and without vegetation) were carbonyl sulfide sinks. Consumption rates varied between 3.6 and 77.7 nmol/m^2-hour; both vegetation and microorganisms contributed to the uptake of carbonyl sulfide. When areas were treated with nitrogen or lime, the

carbonyl sulfide consumption was increased by 30% over the control. A clear cut site took up 3.5 times more carbonyl sulfide than the control, whereas vegetated and water-saturated soils consumed carbonyl sulfide at 43 and 84% higher rates than the non-vegetated and unsaturated soils, respectively (Simmons et al. 2012).

Release of carbonyl sulfide from soils to the atmosphere is influenced by the type of soil as well as soil temperature and water content (Liu et al. 2010). Liu et al. (2007) studied the exchange of carbonyl sulfide between lawn soil and the atmosphere. The uptake of carbonyl sulfide by lawn soil was correlated to temperature; it increased with temperature up to 298°K, and then decreased at higher temperatures. Water content also affected uptake rates, which increased with increasing water content to a maximum of 12.5% and then decreased at higher water levels. The authors concluded that due to the nonlinear relationships of carbonyl sulfide uptake with temperature and water content, carbonyl sulfide content in soil is likely controlled by biological processes. In an experiment, approximately half of the carbonyl sulfide was transformed to water-soluble sulfates by way of hydrogen sulfide (Liu et al. 2007).

Carbonyl sulfide release to the atmosphere from the soil of a temperate spruce forest in the Solling Mountains of Germany was examined in 1999 (Steinbacher et al. 2004). The results indicated a net flux of carbonyl sulfide into the soil from the atmosphere. Uptake rates of the soil were found to be 0.81 pmol/m^2-second on average, with a range of 0.23–1.38 pmol/m^2-second. The authors indicated that the carbonyl sulfide flux was slightly dependent on soil temperature and water content.

Carbonyl sulfide exchange rates were determined in soils from a forest and former rape (*Brassica napus*) field in Germany. When carbonyl sulfide concentrations exceeded 5,000 ppt in the rape field, the uptake rate constant decreased, indicating carbonyl sulfide saturation. When concentrations exceeded 50,000 ppt, the uptake rate constant increased, to which the authors attributed to a second consumption source of carbonyl sulfide. A similar process was found for the forest soil, where the uptake of carbonyl sulfide increased when concentrations were >4,000 ppt. When carbonyl sulfide concentrations were below the compensation concentrations of 785 and 1,470 ppt for the forest and rape field soils, respectively, the soil was considered a source of carbonyl sulfide to the atmosphere (Conrad and Meuser 2000).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Hydrogen Sulfide. Since hydrogen sulfide exists as a gas at atmospheric pressure, partitioning to the air is likely to occur after environmental releases. However, the compound is also soluble in oil and water, and may therefore also partition to surface water, groundwater, or moist soil. In addition, sorption of hydrogen sulfide from air onto soil (Cihacek and Bremner 1993) and plant foliage (De Kok et al. 1983, 1988, 1991) occurs. Hydrogen sulfide's solubility in pure water varies with temperature from 5.3 g/L at 10°C to 3.2 g/L at 30°C. (O'Neil et al. 2001). Once hydrogen sulfide is dissolved in water, it will dissociate into bisulfide ion (HS^-) and sulfide ion (S^{2-}); the ratio of the concentrations of these various ions will depend on the pH of the solution. Hydrogen sulfide can also form insoluble sulfide salts with various metals (i.e., copper, zinc, nickel, and iron) that may be present in soils or environmental waters (Pouliquen et al. 1989).

Hydrogen sulfide evaporates easily from water, and the rate of evaporation depends on factors such as temperature, humidity, pKa, pH, and the concentration of certain metal ions. Hydrogen sulfide will cross the air-water interface with kinetics similar to other unreactive gases (such as oxygen [O_2], nitrogen [N_2], and carbon dioxide [CO_2]) at pH $\leq$6. At higher pH (such as seawater, which has a pH of $\geq$8) hydrogen sulfide escape is enhanced due to an ionic species gradient in the water close to the surface (Balls and Liss 1983). The Henry's law constant was determined under a variety of conditions for hydrogen sulfide dissolved in sewage or distilled water and was found to increase linearly with temperature, indicating an increasing tendency to partition to the gas phase (Al-Haddad et al. 1989; also see Table 4-2). Other factors found to affect the Henry's law constant in sewage were pH, pK, flow rate, and initial hydrogen sulfide concentration. Complexation of bisulfide and sulfide ions to trace metal ions (i.e., Zn^{2+}, Co^{2+}, and Ni^{2+}) found in seawater will also have an effect on the transport of hydrogen sulfide across the air-water interface (Elliott and Rowland 1990).

Clay or organic matter may sorb hydrogen sulfide. Smith et al. (1973) determined the sorption of hydrogen sulfide to six air-dried and moist soils in a laboratory study. The capacities of soil samples to sorb hydrogen sulfide ranged from 15.4 to 65.2 mg/g soil for the air-dried soils and from 11.0 to 62.5 mg/g soil for the moist soils (50% water-holding capacity). Capacities and rates of sorption were not significantly affected by sterilization of the soil sample, indicating that soil microorganisms are not likely to be involved in the sorption process. The authors noted that these values, however, would not provide reliable estimates of the amounts of hydrogen sulfide that could be sorbed by soils under natural

conditions, where the environmental fate of the sorbed hydrogen sulfide would have to be considered. Under natural conditions, it is likely that some of the hydrogen sulfide would be oxidized to sulfate, which may be removed by leaching or taken up by plants. This, in turn, may make gas sorption sites available for additional sorption (Smith et al. 1973). Cihacek and Bremner (1993) showed that soils can sorb considerable amounts of hydrogen sulfide from the air, retaining it as elemental sulfur. Several species of soil, aquatic, and marine microorganisms oxidize hydrogen sulfide to elemental sulfur;,its half-time in these environments usually ranges from 1 hour to several hours (Jørgensen 1982). Food chain bioconcentration and biomagnification are unlikely (HSDB 2013).

Carbonyl Sulfide. Carbonyl sulfide is a significant, non-volcanic source of sulfur in the upper atmosphere due to its long residence time and significant abundance in the troposphere (Blake et al. 2004; Simmons et al. 2012). Carbonyl sulfide can be removed from the atmosphere by terrestrial vegetation, soils, photolysis, and reaction with hydroxyl and oxygen radicals (all of which are considered to be major sinks of carbonyl sulfide) (Blake et al. 2004; Stimler et al. 2010).

Carbonyl sulfide does not adsorb to soils, particularly those rich in organic material, and thus, it may enter groundwater. It is expected to volatilize rapidly from water and both dry and moist soil, and water may leach carbonyl sulfide from soils. When released to water, it will quickly dissipate to air (EPA 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012). Bioconcentration of carbonyl sulfide is not expected in fish or other aquatic organisms, based on an estimated bioconcentration factor ranging from 2 to 11 (EPA 1994c, 1994d; National Iranian Gas Company 2012).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Hydrogen Sulfide. In the atmosphere, hydrogen sulfide may be oxidized by oxygen (O_2) and ozone (O_3) to give sulfur dioxide (SO_2), and ultimately sulfate compounds. Sulfur dioxide and sulfates are eventually removed from the atmosphere through absorption by plants, deposition on and sorption by soils, or through precipitation (Hill 1973). A residence time of approximately 1.7 days at an ozone concentration of 0.05 mg/m^3 has been calculated for hydrogen sulfide (WHO 1981). The effective lifetimes for hydrogen sulfide based on summer daytime and yearly average hydroxyl radical concentrations have been estimated to be 0.23 and 2.3 days, respectively, based a measured rate constant of $4.8x10^{-12}$ cm^3/molecule second (Cox 1975). Lifetimes in air ranging from approximately 1 day in the summer to 42 days in the winter have been estimated for hydrogen sulfide (Bottenheim and Strausz 1980). Hydrogen sulfide is not

expected to be decomposed by direct absorption of ultraviolet radiation and its reaction with ozone is not expected to be a significant environmental fate (Cox 1975).

Carbonyl Sulfide. Carbonyl sulfide is considered to be fairly inert in the troposphere (Liu et al. 2007) and thus has the longest lifetime of an atmospheric sulfur species (Meinrat et al. 1992). It can undergo photolysis and reaction with hydroxyl and oxygen radicals, although both processes have been found to be very slow, or may not occur at all, in the troposphere (Blake et al. 2004; EPA 1994d; GoodGuide 2011; National Iranian Gas Company 2012; Stimler et al. 2010). The lifetime of carbonyl sulfide in the troposphere has been reported as >1 year with a range of 2–10 years (Blake et al. 2004; EPA 1994d; GoodGuide 2011; Liu et al. 2007; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010).

Due to its long residence time in the troposphere, carbonyl sulfide transports into the stratosphere, where photolysis and reaction with oxygen as well as photochemically-produced hydroxyl radicals is thought to be a major route of atmospheric degradation (EPA 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; Stimler et al. 2010). A stratospheric aerosol is formed as a result of these processes which generates a sulfate aerosol layer in the stratosphere that remains present even in the absence of volcanic activity (Conrad and Meuser 2000; Liu et al. 2007; Meinrat et al. 1992; Simmons et al. 2012; Stimler et al. 2010). The sulfate aerosol layer can affect the radiation budget of the earth and may result in increased depletion of the stratospheric ozone layer (Conrad and Meuser 2000; Liu et al. 2007; Meinrat et al. 1992; Simmons et al. 2012). Additionally, carbonyl sulfide is oxidized to sulfur dioxide in the troposphere and/or the stratosphere (which may also have an impact on climate change) (Blake et al. 2004). Carbonyl sulfide can be also removed from the atmosphere by uptake in terrestrial vegetation and soils (Blake et al. 2004; EPA 1994d; GoodGuide 2011; National Iranian Gas Company 2012; Stimler et al. 2010).

6.3.2.2 Water

Hydrogen Sulfide. In aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-) and the second yields sulfide ion (S^{2-}); the pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). At a pH of 7.0, the ratio of the concentration of aqueous hydrogen sulfide to bisulfate ion is approximately 1-to-1. As the pH increases above 7.0, the ratio of the concentration of bisulfide ion to aqueous hydrogen sulfide increases. At a pH of 8, the ratio of the concentration of bisulfide ion to the concentration of aqueous

hydrogen sulfide is approximately 10-to-1. The relative concentration of sulfide ion does not begin to increase until a pH of 11 is exceeded; only above pH 12 will the concentration of sulfide ion become significant (>50%).

Hydrogen sulfide oxidation by O_2 readily occurs in surface waters. At 25°C and pH 8, half-times of 50 and 26 hours were reported for hydrogen sulfide in water and seawater, respectively. Above pH 8, however, the rate of oxidation was independent of pH (Millero et al. 1987). Using a hydrogen peroxide concentration of $1x10^{-7}$ M as found in surface seawater, the half-time for sulfide oxidation by peroxide in seawater would be 2,800 hours. Only at hydrogen peroxide concentrations $>10^{-5}$ M (such as found in rainwaters) would the oxidation of hydrogen sulfide by hydrogen peroxide become competitive with the oxidation by oxygen (Millero et al. 1989). Hydrogen sulfide in waste water may be controlled by addition of oxidizing chemicals, which react to form less toxic byproducts (Tomar and Abdullah 1994). In warm, damp environments (such as manholes and gravity sewers), hydrogen sulfide may be oxidized by autotrophic bacteria to sulfuric acid (Boon 1992). Chemical oxidation of hydrogen sulfide dissolved in sewage water produces sulfur at pH 6–7, while sulfur, polysulfides, thiosulfates, and ultimately sulfate are formed at pH 7–9 (Boon 1992).

Carbonyl Sulfide. Carbonyl sulfide is rapidly removed from water through volatilization. Volatilization of carbonyl sulfide from a model river was found to have an estimated half-life of 2.3 hours (EPA 1994d; National Iranian Gas Company 2012). As it can dissolve in water and does not adsorb well to soils, sediments, or suspended organic matter, carbonyl sulfide may migrate to groundwater (EPA 1994c, 1994d; National Iranian Gas Company 2012).

Carbonyl sulfide was found to hydrolyze slowly in water, where it forms hydrogen sulfide and carbon dioxide (EPA 1994c, 1994d; National Iranian Gas Company 2012; PERC 2001). In the presence of water, carbonyl sulfide is corrosive to metals (HSDB 2007).

6.3.2.3 Sediment and Soil

Hydrogen Sulfide. Hydrogen sulfide is one of the principal components in the natural sulfur cycle. Bacteria, fungi, and actinomycetes (fungus-like bacteria) release hydrogen sulfide during the decomposition of sulfur containing proteins and by the direct reduction of sulfate (SO_4^{2-}). Hydrogen sulfide is also consumed by bacteria found in soil and water that oxidize hydrogen sulfide to elemental sulfur. Photosynthetic bacteria can oxidize hydrogen sulfide to sulfur and sulfate in the presence of light

and the absence of oxygen (EPA 1993; WHO 1981). A number of microorganisms have been found to degrade hydrogen sulfide to elemental sulfur or sulfate. Among these are a heterotrophic bacterium of the genus *Xanthomonas* isolated from dimethyl disulfide-acclimated peat (Cho et al. 1992), heterotrophic fungi (Phae and Shoda 1991), and a marine isopod (Vismann 1991). Soils may sorb considerable amounts of hydrogen sulfide from the air, retaining most of it in the form of elemental sulfur. Manganese compound found in these soils appeared to catalyze the oxidation of hydrogen sulfide to elemental sulfur (Cihacek and Bremner 1993).

Carbonyl Sulfide. Carbonyl sulfide does not adsorb to soils and sediments and will volatilize rapidly from both dry and moist soil. It is highly mobile in soil and may be transported out of soil by water (EPA 1994c, 1994d; National Iranian Gas Company 2012).

Carbonyl sulfide has been found to degrade in soil (Kato et al. 2008). A study by Kato et al. (2008) found that *Mycobacterium* spp. in soil degraded ambient carbonyl sulfide. One strain (THI401) degraded 30 ppm by volume of carbonyl sulfide in 1 hour, decreasing 60% of the initial amount by abiotic conversion in 30 hours. Testing was performed at an ambient carbonyl sulfide concentration of 500 ppt in sterilized soil samples. While it was emitted from the soil during testing, the *Mycobacterium* spp. was found to degrade the carbonyl sulfide more quickly than it was emitted (Kato et al. 2008).

6.3.2.4 Other Media

Carbonyl Sulfide. Uptake of carbonyl sulfide by various biological organisms may be driven by carbonic anhydrase, which is a key enzyme that splits carbonyl sulfide *in vivo* into carbon dioxide and hydrogen sulfide (Liu et al. 2007).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to hydrogen sulfide and carbonyl sulfide depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of hydrogen sulfide and carbonyl sulfide in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on hydrogen sulfide and carbonyl sulfide levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring hydrogen sulfide and carbonyl sulfide in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Hydrogen Sulfide. The concentration of hydrogen sulfide in air can be represented using various concentration units. All air monitoring data reported herein are reported in or have been converted into ppm or ppb for ease of comparison. The conversion factors are: 1 ppm=1.40 mg/m^3 and 1 ppb=1.40 $\mu g/m^3$.

Hydrogen sulfide ambient air concentrations from natural sources have been estimated to be between 0.11 and 0.33 ppb (EPA 1993). In an unpolluted area of Colorado, concentrations between 0.02 and 0.07 ppb were measured (Hill 1973). Near ground level, samples taken around a sulfurous New Zealand lake charged by an active underground geothermal vent had average hydrogen sulfide levels in the range of 0.125–3.9 ppm, which produced no visible adverse effects on indigenous bird or plant populations (Siegel et al. 1986). Hydrogen sulfide concentrations in air in remote marine environments are reported to be highly variable, ranging from 0.001 to 0.1 ppb (Elliott and Rowland 1990). Concentrations of hydrogen sulfide in urban areas are generally <1 ppb (Svendsen 2001). Hydrogen sulfide concentrations >90 ppb were measured during several intermittent periods in the Conimicut Point neighborhood in Warwick, Rhode Island that resulted from rotting seaweed and shellfish from a "die-off" of aquatic plants and animals that occurred in August 2003 in parts of the eastern Narragansett Bay. The concentration of hydrogen sulfide in the residential areas varied over time, depending on the tides, winds, and weather (Fulton et al. 2003).

Indoor air was monitored in five residential homes in the Dakota City/South Sioux City area in Nebraska from April 2 to May 15, 1997. Hydrogen sulfide was routinely found in the indoor air of these homes. In general, hydrogen sulfide was found to not exceed 90 ppb (which was the upper detection limit for the measuring device used in this monitoring study). However, at one home, hydrogen sulfide was found to exceed the upper detection limit for periods of 20 minutes to >3 hours on 10 of the 30 days of sampling (Agency for Toxic Substances and Disease Registry 1997).

Durand and Scott (2005) monitored nine properties in the Rotorua geothermal field area in New Zealand for various geothermal gases, including hydrogen sulfide. These buildings or the site had a history of geothermal gases penetrating to the inside of the buildings. All buildings in this study were found to have chronic contamination of the indoor air by hydrogen sulfide, with the entry of the gas through cracks in floors and subsurface ducts as the most common means of entry. The highest levels of hydrogen sulfide

were reported to be emitted from a vent in a concrete floor of a residential property at 435 ppm. In another location, two interior hydrogen sulfide vents were found, with one vent containing hydrogen sulfide at >200 ppm and the other at 2.9–4.1 ppm (Durand and Scott 2005).

In early 1999, ATSDR and EPA conducted a 12-month hydrogen sulfide monitoring program in Dakota City. Sixteen hydrogen sulfide monitors were stationed in selected locations around the Dakota City area. White et al. (1999) noted that the frequency and concentration of hydrogen sulfide levels in Dakota City were higher than in a typical urban setting. During 6 months in 1999, peak hydrogen sulfide concentrations >90 ppb (the upper detection limit) were recorded at four monitoring locations, and three of these locations had multiple peak concentrations exceeding 90 ppb. Multiple peak levels in the range of 30–50 ppb were recorded for other residential areas. For three monitoring locations that were distant from a known source of hydrogen sulfide, peak levels of 9 and 19 ppb were recorded while most measurements were below the detection limit of 2 ppb (White et al. 1999).

An air monitoring study at a waste water treatment plant in Australia found time-averaged hydrogen sulfide levels of 1–2 ppm near the primary clarifiers and inlet structure, and levels <1 ppm at various other locations in the 10-hectare plant site (Koe 1985). Hydrogen sulfide was not detected by air-sampling instruments located around the perimeter of a landfill in Ohio after a major landslide occurred in March 1996 (Ingram et al. 1997). In a study to determine the quantity and composition of reduced sulfur gases (including hydrogen sulfide) being released to the atmosphere at waste water treatment plants in Baton Rouge, Louisiana at various steps of the treatment process, hydrogen sulfide was found to be the dominant sulfur compound emitted. The concentrations of hydrogen sulfide were typically <7.5 ppm sulfur, with concentrations ranging from 0.013 ppm sulfur (central treatment plant final effluent box) up to 340 ppm sulfur (central treatment plant digester dome of the floating roof) (Devai and DeLaune 1999). The hydrogen sulfide concentration in the atmosphere of a Norwegian sewage purification plant was generally below 2 ppm; however, a peak concentration of 100 ppm was detected (Søstrand et al. 2000). As part of the 1997 Fresh Kills Air Monitoring Program, >140,000 observations of ambient air were collected over a 2-month period at 16 locations on Staten Island, New York. Hydrogen sulfide was measured at detectable levels in only about half of the samples, with measured levels ranging from 2 ppb (the detection limit) to 33 ppb (Agency for Toxic Substances and Disease Registry 2000).

Hydrogen sulfide concentrations in air can vary widely during manure management activities. Levels of hydrogen sulfide in air in pig barns during normal operations are generally <5 ppm. However, concentrations can rapidly rise up to 800 ppm inside manure transfer pits or lift stations when the manure

is agitated; additionally, the hydrogen sulfide can back up into pig rooms through open pits or piping. Concentrations of hydrogen sulfide have been shown to increase from very low levels to 1,300 ppm in deep-pit buildings when manure is agitated (Chénard et al. 2003).

The concentrations of sulfur compounds (including hydrogen sulfide) were measured in the air at four paper pulp mills using the kraft (sulfate) process. In this process, steam, high temperature, high pressure, and a solution containing sodium hydroxide and sodium sulfide are used to digest wood chips. Various sulfur gases are produced during this process. Hydrogen sulfide concentrations ranged from not detected (<0.2 ppm) to 35 ppm at various emission sources in the continuous digester, batch digester, and pulp washing areas. In general, hydrogen sulfide was not detected in ambient air sampled at these plants (Goyer 1990). A survey of occupational exposure in nonproduction departments of pulp, paper, and paper product mills from 147 mills in 11 countries found that hydrogen sulfide was below the detection limit in 45% of the 20 measurements taken at 6 mills. A mean concentration of 2.9 ppm was reported, with a maximum value of 53 ppm and a lowest detected value of 0.04 ppm (Teschke et al. 1999). The concentrations of various pollutants were measured in the air of five textile factories (which included three weaving and dyeing factories and two clothing factories); hydrogen sulfide concentrations ranged from <0.007 to 1.32 ppm (Rimatori et al. 1996).

Ten air samples were collected for hydrogen sulfide at the World Trade Center disaster site in New York City between September 18 and October 4, 2001. Concentrations ranged from not detected (3 of the 10 samples) to 3.0 ppm (Wallingford and Snyder 2001).

Some U.S. homes built between 2001 and 2008 contain imported drywall, also known as “Chinese drywall or problem drywall”. The U.S. Consumer Product Safety Commission conducted an emission and corrosion study of 51 homes. Indoor air concentrations of hydrogen sulfide was significantly higher in homes reporting drywall-related complaints with a mean concentration of 0.66 ppb (0.19–2.33 ppb) compared with a mean concentration 0f 0.45 ppb (0.2–2.23 ppb) in non-complaint homes (CPSC 2010a).

Carbonyl Sulfide. Carbonyl sulfide is the most prevalent, longest-lived sulfur-containing gas in the troposphere (Blake et al. 2004; Conrad and Meuser 2000; Meinrat et al. 1992; Stimler et al. 2010). Global mean concentrations in the troposphere have been reported as 500–510 ppt (Blake et al. 2004; Conrad and Meuser 2000; Meinrat et al. 1992).

Carbonyl sulfide concentrations in the ambient air were reported for several urban and suburban areas in the United States. The mean concentration from 1977 to 1982 was reported as 1.2 μg/m^3 (0.49 ppb), with concentrations ranging from 1.0 to 1.4 μg/m^3 (0.41–0.57 ppb) (GoodGuide 2011). Rural and urban sites in the United States near natural sources of carbonyl sulfide were also sampled. Air concentrations in the rural areas ranged from 0.27 to 0.80 μg/m^3. Concentrations of carbonyl sulfide in air from urban areas were as follows: 1.17 μg/m^3 (Philadelphia, Pennsylvania), 1.21 μg/m^3 (Wallops Island, Virginia), 1.37 μg/m^3 (Lawton, Oklahoma). Carbonyl sulfide air concentrations over salt marshes (one of the main natural sources of carbonyl sulfide) ranged from approximately 60 to 180 μg/m^3, while air samples from over the ocean ranged from 14 to 19 μg/m^3 (EPA 1994d).

Carbonyl sulfide concentrations in air were measured over the western pacific and Asia in the spring of 2001. Concentrations over the western Pacific were found to decrease 10% from the surface to 8–10 km in altitude. It was thought that terrestrial carbonyl sources dominated the output during the springtime of that year. A mean carbonyl sulfide concentration of 580 ppt was measured below 2 km in altitude near the coast of Asia, which coincided with the area where air from urban Asia had the most impact (Blake et al. 2004).

Rasmussen et al. (1982a) collected air samples in both the North Atlantic and Pacific oceans. The concentrations of carbonyl sulfide from the samples were nearly uniform, and thus, an average value of 472±86 ppt was reported (Rasmussen et al. 1982a).

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and hazardous air pollutants monitoring data. Detailed air monitoring data for carbonyl sulfide in various states for 2005 are shown in Table 6-2. Data for other years are available as zipped Microsoft Access database files that may be accessed directly from the EPA website. In general, the average concentration of carbonyl sulfide in outdoor air is approximately 1.8 ppb for the majority of the U.S. locations sampled. A maximum concentration of approximately 18 ppb was identified (EPA 2013e).

6.4.2 Water

Hydrogen Sulfide. Hydrogen sulfide readily evaporates from surface waters and is not likely to persist in highly oxygenated waters; levels in these environments are expected to be low. Groundwater samples from an area receiving acid-mine drainage in Colorado averaged 0.9 ppm of hydrogen sulfide, while samples from a power plant site averaged 0.03 ppm (Patterson and Runnells 1992).

Table 6-2. 2005 Average Air Monitoring Data from Air Quality System for Hydrogen Sulfide

Number of samples	Concentration (ppm/1 hour)	State[a]
7,721	0.001936377	MT
7,813	0.001015573	IA
8,318	0.001008929	TX
8,681	0.00101984	IA
5,411	0.001136588	TX
8,284	0.001095597	IA
7,748	0.001245654	TX
8,705	0.001735431	MO
8,141	0.00181049	OK
8,672	0.001	IA
8,535	0.001049927	CA
8,301	0.001001434	CA
8,408	0.001405574	PA
6,460	0.002279191	KS
8,233	0.002	CA
8,271	0.001	CA
8,404	0.001014526	CA
8,232	0.002598714	MT
7,896	0.001	TX
8,435	0.001214977	OK
5,676	0.001224753	TX
8,283	0.001	CA
8,111	0.001041906	IA
8,136	0.001062026	IA
7,931	0.004175733	CA
8,695	0.001079153	IA
8,579	0.001035658	PA
8,713	0.001076397	CA
8,625	0.001146667	IA
7,782	0.017780267	TX
8,655	0.001	CA
6,305	0.00106765	IA
8,312	0.001048919	IA

[a]Post Office abbreviations used.

Source: EPA 2013e

Accurate measurements of hydrogen sulfide water levels are usually complicated by the presence of other sulfide compounds. At pH ≥7, hydrogen sulfide is significantly dissociated, and the exact source of sulfide would not necessarily be known. A method of determining sulfide concentration in unspecified waste water by first transforming it to hydrogen sulfide and then measuring the atomic absorption of the product yielded results ranging from 3.1 to 5.1 ppm of sulfide sulfur (Parvinen and Lajunen 1994). Total sulfide levels in samples from the Mississippi River were about 0.92 ppm, while levels in pond and well water in St. Paul, Minnesota were 1.6 and 1.9 ppm, respectively (Slooff et al. 1991).

Nearshore hydrogen sulfide eruptions occur in the Atlantic Ocean along the central coast of Nambia. Dissolved hydrogen sulfide concentrations were found to range from <0.02 to 3.39 ppm in water sampled at various depths during eruption events that occurred during 2001–2002 (Weeks et al. 2004).

Carbonyl Sulfide. Surface water samples from temperate and subtropical North Atlantic regions and the Gulf of Mexico were found to be supersaturated with carbonyl sulfide with respect to atmospheric equilibrium. Carbonyl sulfate concentrations followed a diel pattern. The highest concentrations were measured in coastal and shelf water samples. Concentrations of carbonyl sulfide were determined for various biogeographic regions, including oligotrophic, transition, upwelling, and coastal/shelf as 13, 24, 27, and 112 pmol/L, respectively. Fluxes for the same regions were calculated as 0.9, 1.6, 2.3, and 7.9 Gmol/L, respectively. The total carbonyl sulfide concentration from the study was determined to be 32 pmol/L. The total flux of carbonyl sulfide to the atmosphere from the oceans was estimated to be 12.7 Gmol/year (0.41 Tg sulfur/year). The authors found that the concentration as well as the flux of carbonyl sulfide between the ocean and the atmosphere was highly dependent on marine productivity (Meinrat et al. 1992).

Carbonyl sulfide has also been identified in waste water at treatment plants. Carbonyl sulfide, along with hydrogen sulfide and methyl mercaptans, are responsible for the odors that emanate from such facilities (Sattler and Rosenberk 2006).

6.4.3 Sediment and Soil

Hydrogen Sulfide. Hydrogen sulfide levels as high as 11.7 ppm in soil water were measured in Louisiana rice fields (Hollis 1985). The hydrogen sulfide in these samples was presumably bound to colloidal clay or organic matter, as these levels were higher than typical solubility would predict and were not accompanied by the characteristic hydrogen sulfide odor. Sediment pore water from the Grand

Calumet River in an industrialized area of Indiana contained 0.2–1.5 ppb of hydrogen sulfide (Hoke et al. 1993). In general, undisturbed anoxic sediment pore water may contain up to 100 ppb hydrogen sulfide, while disturbed sediments typically contain pore water concentrations of 1–30 ppb (Dillon et al. 1993).

Carbonyl Sulfide. Carbonyl sulfide concentrations in soil from a forested area and a former rape (*B. napus*) field were found to range from 250 to 120,000 ppt (Conrad and Meuser 2000).

6.4.4 Other Environmental Media

Hydrogen Sulfide. Hydrogen sulfide is commonly found in coal, petroleum, and natural gas deposits and may be mobilized by human manipulation of these resources. Coal gasification (a process whereby coal is subjected to heat and steam treatment to produce a convenient energy source) results in a gas product consisting of up to 1% hydrogen sulfide (Barik et al. 1987). Hydrogen sulfide was identified as a component in the vapor phase of cigarette smoke (Dong et al. 2000), and was found in the emissions of gasoline vehicles (Collier et al. 2002).

Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization. Similar chemical reactions may explain the presence of hydrogen sulfide in dental plaque (Tonzetich and Carpenter 1971). Meat products may be contaminated with hydrogen sulfide-producing bacteria, resulting in off-odors and spoilage (McMeekin and Patterson 1975).

Hydrogen sulfide is produced in the large intestine of mammals by metabolism of sulfhydryl proteins by anaerobic bacteria, and may compose up to 10% of intestinal gases (Beauchamp et al. 1984; EPA 1978). Hydrogen sulfide was found in the gas produced by feces of infants; levels were found to vary based on the types of diets the infants were fed and the age of the infants. Fecal gas production for infants aged 1–3 months was 372–833, 73–371, and 1,904–2,540 nmol/g (12.7–28.3, 2.5–12.6, and 65.8–86.4 μg/g) dry weight for infants fed breast milk, milk-based formula, and soy based formula, respectively (Jiang et al. 2001). Fecal sulfide concentrations in 15 adult volunteers ranged from 110 to 720 nmol/g (3.74–24.5 μg/g) wet weight. Fecal sulfide concentrations were found to increase significantly from 160 to 750 nmol/g (5.4–26 μg/g) when subjects were fed diets containing increasing amounts of meat. Sulfide concentrations in whole-blood samples from six healthy adults were found to range from 10 to 100 μmol/L (0.3–3 μg/mL). When increasing amounts of protein from meat were added to the diet of

these subjects, blood sulfide concentrations did not change significantly (Richardson et al. 2000). Hydrogen sulfide is also produced in the human mouth by microbial putrefaction (Rosenberg et al. 1991). Mean sulfide levels in human brainstem controls were reported as 0.69 and 0.59 µg/g for males (n=36) and females (n=9), respectively. Sulfide concentrations of 0.91 and 1.04 µg/g were reported in brainstems from two suspected hydrogen sulfide inhalation fatalities (Goodwin et al. 1989). Concentrations of sulfide in the blood, brain, lung, and femoral muscle of a victim of a fatal hydrogen sulfide poisoning were 0.45 µg/mL, 2.72 µg/g, 0.42 µg/g, and 0.16 µg/g, respectively. The victim was kept at 0°C until autopsy, 20 hours after death; these conditions were expected to significantly suppress sulfide production due to putrefaction (Kage et al. 1998). Blood sulfide levels at 4 µg/mL were found in an individual who died while working at a treatment, storage, and disposal facility for hazardous waste materials. Sulfide levels were also analyzed in tissue samples and confirmed that the blood sulfide concentrations could not be attributed to cellular decay. Through an investigation by OSHA, it was determined that high concentrations of hydrogen sulfide were apparently generated during the waste acid neutralization process (Smith and Cummins 2004).

Hydrogen sulfide was detected in emission testing of drywall samples. In the 30 samples, hydrogen sulfide emissions ranged from not detected to 200.60 µg-S/m^2/hour) (CPSC 2010b).

Carbonyl Sulfide. Emission tests of drywall samples have detected a number of reactive sulfur compounds, including hydrogen sulfide and carbonyl sulfide. The levels of carbonyl sulfide in the 30 drywall samples tested ranged from not detected to 4.25 µg-S/m^2/hour (CPSC 2010b).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Hydrogen Sulfide. Primary exposure of the general population to hydrogen sulfide most likely occurs through inhalation of ambient air. As hydrogen sulfide is part of the natural environment, the general population will have some exposure to hydrogen sulfide. Hydrogen sulfide is produced in the human large intestine by the bacterial reduction of inorganic sulfate and sulfite, and by fermentation of sulfur-containing amino acids, cysteine, and methionine (Richardson et al. 2000); it can compose up to 10% of intestinal gases (EPA 1978). Hydrogen sulfide is produced by the natural bacteria found in the human mouth, and is a component of bad breath (halitosis) (Rosenberg et al. 1991).

Hydrogen sulfide may occur naturally in well water, and can be formed in hot water heaters, giving household hot tap water an unpleasant odor. Formation of hydrogen sulfide can occur by the reduction of

sulfates in the water by sulfur bacteria (which can thrive in the warm environment of the hot water heater) or by reaction with the magnesium anode in the hot water heater tank (MDH 2004). Populations living in areas of geothermal activity, near waste sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, landfills, manure treatment facilities, waste water treatment facilities, and tanneries may be more likely to be exposed to higher levels of hydrogen sulfide. Geothermal gases (including hydrogen sulfide) were found to be entering buildings in Rotorua, New Zealand directly from the ground through floors, walls and subsurface pipes; indoor vents emitting up to approximately 200 ppm were reported (Durand and Scott 2005). The general population may also be exposed to hydrogen sulfide by accidental release ("blowout") from natural gas wells during drilling operations near residential areas (Layton and Cederwall 1986; Leahey and Schroeder 1986). Exposures to hydrogen sulfide have occurred through the mixing of acid and basic drain cleaners and through the use of acid drain cleaner to remove sludge-clogged drains, but these incidents are thought to be rare (Oderda 1975).

Residents of the Conimicut Point neighborhood in Warwick, Rhode Island were exposed to hydrogen sulfide from rotting seaweed and shellfish caused by a "die-off" of aquatic plants and animals that occurred on August 20, 2003 in parts of the eastern Narragansett Bay. The concentration of hydrogen sulfide in the residential areas varied over time, depending on the tides, winds, and weather. During the week of September 15, 2003, the Rhode Island Department of Environmental Management measured several intermittent periods when hydrogen sulfide concentrations were >90 ppb (Fulton et al. 2003). Emissions from the Fresh Kills Landfill on Staten Island, New York, which contain hydrogen sulfide, are blown by prevailing wind into nearby neighborhoods (Agency for Toxic Substances and Disease Registry 2000).

Workers may be occupationally exposed to hydrogen sulfide from fermenting manure (Chénard et al. 2003; Morse et al. 1981), stagnant wells (McDonald and McIntosh 1951), areas of waste-water treatment facilities (NIOSH 1980b, 1984, 1985a, 1985d, 1990), extruded rubber plants (NIOSH 1985b), landfills (Lehman 1996), textile industries (Rimatori et al. 1996), and petroleum refineries (NIOSH 1982a, 1982b). Facilities where hydrogen sulfide can be generated include petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, viscose rayon manufacturing plants, sulfur production facilities, iron smelters, food processing plants, and tanneries (Svendsen 2001). Major occupational exposures to hydrogen sulfide have resulted from its presence as a byproduct of chemical reactions that may take place in viscose rayon and leather tanning processes (ACGIH 1991). Hydrogen sulfide is also used as an agricultural disinfectant and as an additive in lubricants and cutting oils

(Bingham et al. 2001; HSDB 2013; Sittig 2002). Hydrogen sulfide may also be encountered in various industrial processes including the manufacture of dyes and pigments, felt, rayon and artificial silk; in brewing, glue making, and rubber vulcanization; and in lithography and photoengraving (Beck et al. 1981; Grant and Schuman 1993; Sittig 2002). Hydrogen sulfide levels were measured using personal monitors worn by farm workers in Norway during 1992–1996 while performing various tasks, such as handling of harvest, tending to animals, and handling of manure. Hydrogen sulfide was only detectable in 7 out of 23 measurements with a range of peak values of 0.2–6 ppm (Eduard et al. 2001).

In the most recent annual report of national poison control centers (2012) compiled from 57 centers, there were 809 reports of hydrogen sulfide exposure (Mowry et al. 2013). Approximately 42% of the exposures resulted in no or minor outcomes, 12% had moderate outcomes, 1.6% had major outcomes, and there were five deaths (0.6%). The numbers of reported hydrogen sulfide exposures were higher in the 2010 (1,054 cases), 2005 (1,396 cases), 2000 (1,382 cases), and 1995 (1,407 cases) annual reports (Bronstein et al. 2011; Lai et al. 2006; Litovitz et al. 1996, 2001). The outcome severity was similar for the different reporting years, with the exception that no deaths were reported in 1995.

Carbonyl Sulfide. Exposure of the general population to carbonyl sulfide is primarily through inhalation of ambient air (National Iranian Gas Company 2012). Carbonyl sulfide is a component of the global sulfur cycle and exists in the atmosphere at high concentrations (Conrad and Meuser 2000; Meinrat et al. 1992; Simmons et al. 2012; Stimler et al. 2010; Wright 2000). It is released to the atmosphere from various natural and anthropogenic sources, including wetlands, soil, trees, volcanic gases, oceans, biomass burning, aluminum production, combustion of coal, extraction of gas and oil, automobiles, and chemical processing, among others (ASTM International 2012; Blake et al. 2004; EPA 1994c, 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; PERC 2001; Rasmussen et al. 1982a, 1982b; Stimler et al. 2010). Due to these numerous sources, there is constant exposure to low levels of carbonyl sulfide (Wright 2000). The frequency and duration of exposure influences the effect carbonyl sulfide has on human health (EPA 1994c).

Carbonyl sulfide may be used as a fumigant for commodities and structures, which could potentially result in exposure to the general population. Wheat, oats, barley, and canola (which have natural, background carbonyl sulfide levels ranging from 0.05 to 0.1 mg/kg) can be treated with carbonyl sulfide to increase insect resistance. An Australian study, however, found that post fumigation carbonyl sulfide residues used in wheat, oat, barley, and canola field trials were less than the Australian maximum residue level of 0.2 mg/kg after being aired for 4 hours. Consequently, the study concluded that carbonyl sulfide

is completely removed from commodities after fumigation and concentrations in grains and seeds are not discernible from levels in untreated grains. Carbonyl sulfide is rapidly desorbed after fumigation (Wright 2000). Exposure may also result from natural levels of carbonyl sulfide found in foods, such as cheese and vegetables in the cabbage family (Wright 2000).

In occupational settings, exposure to carbonyl sulfide is mainly inhalation from its production and use as a chemical intermediate (EPA 1994d), such as in the viscose rayon industry (GoodGuide 2011). It is also a byproduct in petroleum refining and coal distillation, and thus, workers in gas production and distribution facilities may be exposed to carbonyl sulfide in higher concentrations than the general public (GoodGuide 2011). As carbonyl sulfide targets the central nervous system and can result in narcotic effects and respiratory paralysis (Chase et al. 2010; Lewis 2007), monitoring is important to warn those in enclosed facilities of carbonyl sulfide releases (Chase et al. 2010).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Hydrogen Sulfide. Hydrogen sulfide is found naturally in crude petroleum, natural gas, volcanic gases, hot springs, and often as the result of bacterial breakdown of organic matter. Children may be exposed to hydrogen sulfide if they live or play near animal waste sites including places where there might be sediments of fish aquaculture, livestock barns, or manure areas. Inhalation is the most likely route of exposure, and there are no known hydrogen sulfide exposure pathways generally unique to children; hydrogen sulfide is heavier than air (which may increase their risk of exposure to higher concentrations

than adults). Children living in areas of geothermal activity, near waste sites or industries such as petroleum refineries, natural gas plants, petrochemical plants, coke oven plants, kraft paper mills, food processing plants, and tanneries are more likely to be exposed to higher levels of hydrogen sulfide due to physiological and behavior factors previously mentioned. Geothermal gases (including hydrogen sulfide) were found to be entering buildings in Rotorua, New Zealand directly from the ground through floors, walls, and subsurface pipes; indoor vents emitting up to approximately 200 ppm were reported. This concentration is high enough to present an acute respiratory hazard to persons close to the vent, such as children playing on the floor (Durand and Scott 2005). In a clinical case involving a 20-month-old child whose parents lived beside a coal mine where a burning tip had been emitting hydrogen sulfide for nearly 1 year, the patient had symptoms of ataxia and an abnormal CT scan of the brain (Gaitonde et al. 1987). Monitoring data showed that the hydrogen sulfide levels in the air were approximately 0.6 ppm, but may have been higher before data were collected.

Hydrogen sulfide is also produced by bacteria in the mouth and gastrointestinal tract. Hydrogen sulfide formation has been demonstrated in pediatric intravenous amino acid solutions used to treat infants with high protein requirements (Decsi and Koletzko 1993). Levels up to 1.96 ppm were found, presumably formed by sulfide liberation from cysteine derivatives during heat sterilization.

There are no known studies in which hydrogen sulfide levels were measured in the blood or other tissues of children. Hydrogen sulfide was found in the gas produced by feces of infants, and levels were found to vary based on the types of diets the infants were fed and the age of the infants. Fecal gas production for infants aged 1–3 months were 372–833, 73–371, and 1,904–2,540 nmol/g (12.7–28.3, 2.5–12.6, and 65.8–86.4 μg/g) dry weight for infants fed breast milk, milk based formula, and soy based formula, respectively (Jiang et al. 2001).

It is not clear whether hydrogen sulfide can be transferred from mother to fetus. There is limited evidence that women occupationally exposed to hydrogen sulfide have a higher rate of spontaneous abortions. Women employed in rayon textile and paper products jobs in Finland were found to have an increased rate of spontaneous abortions when the mean annual level of hydrogen sulfide exceeded 3 ppb (Hemminki and Niemi 1982). An increase in spontaneous abortions was also found in women working in petrochemical plants in China as compared to women working in non-chemical plants (Xu et al. 1998).

Carbonyl Sulfide. As carbonyl sulfide exists in the atmosphere due to both natural and anthropogenic sources, children can be exposed through inhalation of ambient air (Conrad and Meuser 2000; Meinrat et

al. 1992; National Iranian Gas Company 2012; Simmons et al. 2012; Stimler et al. 2010; Wright 2000). Natural sources, such as soils and oceans, as well as human activities (including combustion of coal, automobile use, and chemical processing) can introduce carbonyl sulfide to the air (ASTM International 2012; Blake et al. 2004; EPA 1994c, 1994d; Meinrat et al. 1992; National Iranian Gas Company 2012; PERC 2001; Rasmussen et al. 1982a; Stimler et al. 2010). Children are therefore exposed to a constant, low level of carbonyl sulfide (Wright 2000). The main exposure concerns are typically associated with occupational settings where carbonyl sulfide is produced and used (such as for a chemical intermediate [EPA 1994d]), and in this context, childhood exposure may be limited.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Hydrogen Sulfide. Workers employed at facilities that manufacture or use hydrogen sulfide in the production process are especially prone to exposure. Such industries include the manufacture of rayon textiles, lubricants, pulp and paper, and sulfuric acid and inorganic sulfides. Workers in facilities where hydrogen sulfide is produced as a byproduct (such as farms with manure storage pits, petroleum or natural gas drilling operations, landfills, and waste water treatment plants) may also be exposed to high levels of hydrogen sulfide.

Carbonyl Sulfide. People in occupational settings where carbonyl sulfide is used and produced are likely to have the highest rates of exposure. In particular, workers in a facility where carbonyl sulfide is used as a chemical intermediate are particularly at risk of exposure (EPA 1994d). Those in the petroleum refining, gas production and distribution facilities, and coal distillation fields may be exposed to carbonyl sulfide in higher concentrations than the general public (GoodGuide 2011). Working with carbonyl sulfide in an enclosed facility increases the likelihood of exposure during a release (Chase et al. 2010).

6.8 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 and carbonyl sulfide is available. Where adequate information is not available, ATSDR, in conjunction with 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 and carbonyl 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.

6.8.1 Identification of Data Needs

Physical and Chemical Properties.

Hydrogen Sulfide. Information is available on the physical and chemical properties of hydrogen sulfide (Al-Haddad et al. 1989; Amoore and Hautala 1983; Daubert and Danner 1989; HSDB 2013; NIOSH 2011; O'Neil et al. 2001). However, additional information on those properties that determine the specific fate, transport, and rates of transformation of hydrogen sulfide as part of the larger sulfur cycle would be useful in discerning the environmental fate and behavior of this compound.

Carbonyl Sulfide. Physical and chemical properties of carbonyl sulfide are reasonably well characterized (EPA 1994c; HSDB 2007; Lewis 2007).

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986 (42 U.S.C. Section 11023), industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2011, became available in November of 2012. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate.

Hydrogen Sulfide. Hydrogen sulfide is known to easily evaporate into the air (EPA 1993; Layton and Cederwall 1986; Leahey and Schroeder 1986), although its solubility in water may also cause it to persist in unperturbed, anoxic sediments. Additional information on the transport, transformation, and persistence of the compound in soils and groundwater (particularly at hazardous waste sites) would be useful in identifying the most important routes of human exposure to hydrogen sulfide.

Carbonyl Sulfide. Likewise, carbonyl sulfide is typically released to air, where it is highly abundant (Conrad and Meuser 2000; Meinrat et al. 1992; Simmons et al. 2012; Stimler et al. 2010). Additional information concerning the transport, transformation, and persistence of carbonyl sulfide in soils and water would be useful.

Bioavailability from Environmental Media. Additional information on absorption following dermal contact with, or ingestion of, contaminated soil and water would also be helpful in determining the importance of this route of exposure for populations of concern for both hydrogen sulfide and carbonyl sulfide.

Food Chain Bioaccumulation.

Hydrogen Sulfide. Sufficient information is available to demonstrate that hydrogen sulfide is not likely to bioaccumulate or biomagnify in the food chain.

Carbonyl Sulfide. While carbonyl sulfide is not expected to bioconcentrate in aquatic organisms (EPA 1994c, 1994d; National Iranian Gas Company 2012), additional experimental data in support of this would be useful.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of hydrogen sulfide and carbonyl sulfide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hydrogen sulfide and carbonyl sulfide in the environment can be used in combination with the known body burden of hydrogen sulfide and carbonyl sulfide to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Hydrogen Sulfide. Monitoring of hydrogen sulfide levels in ambient air is currently sporadic; additional, more systematic sampling is needed, particularly in areas that may have a significant source of hydrogen sulfide. Methods for accurately measuring dissolved sulfides in water are also available (APHA 1998). As hydrogen sulfide is a weak acid, concentrations of aqueous hydrogen sulfide will depend on the pH of the solution. The concentration of un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components, the pH of the solution, and the acidity constants for hydrogen sulfide (APHA 1998). Reliable monitoring data for the levels of hydrogen sulfide in contaminated media at hazardous waste sites are needed so that the information obtained on levels of hydrogen sulfide in the environment can be used in combination with the known body burdens of hydrogen sulfide to assess the

potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. More data on the levels of hydrogen sulfide at the point of emission (on-site) versus levels at the point of exposure (off-site) would be useful.

Carbonyl Sulfide. Likewise, while monitoring data in air exist for carbonyl sulfide, experimental data for concentrations in water and soil would be useful.

Exposure Levels in Humans.

Hydrogen Sulfide. Occupational studies often do not report exposure levels. Additional information is needed on the exposure levels among populations living in the vicinity of hazardous waste sites and other potential sources of hydrogen sulfide, such as hot springs and waste water treatment plants.

Carbonyl Sulfide. For carbonyl sulfide, exposure levels in occupational settings would be useful.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. The only information that provided an assessment of exposure of children and adolescents to hydrogen sulfide was that developed during the South Karelia Air Pollution Study in southeastern Finland where there are a cluster of pulp mills using the sulfate method (Marttila et al. 1994b); however, determining the magnitude of these exposures was complicated by the study's analysis of only gross sulfur concentrations rather than measuring the concentrations of individual sulfur-containing compounds and particulates. Additional exposure information is needed from communities where only hydrogen sulfide exceeds background levels. No exposure studies directly related to children were found for carbonyl sulfide. Additional information identifying the risks specific to children would be useful.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children’s Susceptibility.

Exposure Registries. No exposure registries for hydrogen sulfide or carbonyl sulfide were located. These substances are not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. These substances will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National

Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

6.8.2 Ongoing Studies

No ongoing studies were located for hydrogen sulfide or carbonyl sulfide.

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring hydrogen sulfide and carbonyl sulfide, their metabolites, and other biomarkers of exposure and effect to hydrogen sulfide and carbonyl sulfide. The intent is not to provide an exhaustive list of analytical methods, but to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Hydrogen Sulfide. A limited number of analytical techniques have been used for measuring hydrogen sulfide in the breath (expired air) and sulfide in biological tissues and fluids including blood and saliva. These include gas chromatography coupled with flame ionization detection (GC/FID), gas chromatography coupled with flame photometric detection (GC/FPD), iodometric titration, potentiometry with ion-selective electrodes (ISE), spectrophotometry, and high-performance liquid chromatography (HPLC). The measurement of sulfide concentrations in biological materials is difficult due to its volatility, tendency to undergo oxidation, adsorption to glass and rubber, and binding to organic molecules (Richardson et al. 2000). Details of commonly used analytical methods for several types of biological media are presented in Table 7-1.

In air, hydrogen sulfide will exist in its molecular form, and methods are available to measure hydrogen sulfide in air. However, in aqueous solution, hydrogen sulfide is a weak acid, exhibiting two acid dissociation constants. The first dissociation yields bisulfide ion (HS^-) and the second yields sulfide ion (S^{2-}), with pK_a values for each of these dissociations of 7.04 and 11.96, respectively (O'Neil et al. 2001). In biological tissues and fluids, sulfide concentrations typically would be determined. The concentration of the un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components (e.g., HS^-, S^{2-}), pH of the solution, and acidity constants for hydrogen sulfide using the following equilibrium expressions for the ionization of hydrogen sulfide and bisulfide ion (APHA 1998):

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Blood	Hydrogen sulfide is generated in Kipp's apparatus and trapped in NaOH solution; pH is adjusted to 6.5–6.8, azide and excess iodine are added.	Iodometric method	4 µg/L	98–102	Puacz et al. 1995
Blood	Hydrogen sulfide is generated in Kipp's apparatus and trapped in NaOH solution; sulfide antioxidation buffer is added.	Potentiometry (ISE)	NR	98–102	Puacz et al. 1995
Blood	Liberation of blood sulfide by addition of acid; trapping of hydrogen sulfide gas in NaOH solution.	ISE	10 µg/L	NR	Lindell et al. 1988
Blood and urine	For thiosulfate detection, add 0.2 mL sample to mixture of 0.5 mL of 20 mM PFBBr solution in acetone, 0.05 mL of 5% sodium chloride. Vortex for 1 minute and add 2 mL of 25 mM iodine solution in ethyl acetate and 0.5 mL of internal standard solution (40 µM TBB in ethyl acetate). Vortex for 30 seconds and centrifuge at 2,500 rpm for 15 minutes, allow to stand for 1 hour.	GC/ECD	3 µmol/L	NR	Kage et al. 1997
Blood and urine	For sulfide detection, add 0.2 mL sample to mixture of 0.5 mL of 20 mM PFBBr solution in toluene, 2.0 mL of internal standard solution (10 µM TBB in ethyl acetate), and 0.8 mL of 5 mM tetradecyl-dimethylbenzyl ammonium chloride solution in oxygen-free water saturated with sodium tetraborate. Vortex 1 minute, add 0.1 g potassium dihydrogenphosphate as a buffer. Vortex for 10 seconds, centrifuge at 2,500 rpm for 10 minutes.	GC/ECD	0.3 µmol/L	NR	Kage et al. 1997

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Urine	Freeze and store freshly voided urine samples at -25°C until analysis within 24 hours after exposure. Analyze urinary thiosulfate as its bromobimane product. Correct results for the excreted creatinine analyzed in the same samples.	LC	NR	92, 80	Kangas and Savolainen 1987
Blood and feces	Addition of zinc acetate to trap sulfide, followed by micro-distillation into NaOH solution to trap evolved hydrogen sulfide; analysis by ion chromatography.	IC/ECD	2.5 µmol/L	92–102 (feces) 79–102 (blood)	Richardson et al. 2000
Breath	Connect Teflon sampling probe to analyzer and syringe through sampling valve and loop; insert probe 4 cm into mouth between closed lips; withdraw 20 mL over 6 seconds into syringe; flush and fill the sample loop with 10 mL mouth air; carry sample to analysis in nitrogen gas.	GC/FID	10 µg/m^3 (7 ppb)	NR	Blanchette and Cooper 1976
Breath	Collect air from breathing zone using a midget impinger containing calcium hydroxide-calcium sulfide-arabinogalactan slurry; add solution of N,N-dimethyl-p-phenylene-diamine and ferric chloride.	Spectro-photometry	0.20 µg/m^3 (0.1 ppb)	80	NIOSH 1977a
Saliva	Collect 3 mL aliquot with sterile pipette; introduce into 2-ounce glass container and cap; incubate 24 hours at 37°C; withdraw through cap with gas-tight syringe.	GC/FID, microcoulo-metric titration	NR	NR	Solis and Volpe 1973

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Brain, lung, and femoral muscle	For sulfide detection, add 0.2 g sample (minced) to mixture of 0.5 mL of 20 mM PFBBr solution in toluene, 2.0 mL of internal standard solution (10 µM TBB in ethyl acetate), and 0.8 mL of 5 mM tetradecyl-dimethylnenzyl ammonium chloride solution in oxygen-free water saturated with sodium tetraborate. Vortex 1 minute, add 0.1 g potassium dihydrogenphosphate as a buffer. Vortex for 10 seconds, centrifuge at 2,500 rpm for 10 minutes.	GC/MS	NR	NR	Kage et al. 1998
Brain, lung, and femoral muscle	For thiosulfate detection, add 0.2 g sample (minced) to mixture of 0.5 mL of 20 mM PFBBr solution in acetone, 0.05 mL of 5% sodium chloride and 0.5 mL of 200 mM L-ascorbic acid. Vortex for 1 minute and add 2 mL of 25 mM iodine solution in ethyl acetate and 0.5 mL of internal standard solution (40 µM TBB in ethyl acetate). Vortex 30 seconds and centrifuge at 2,500 rpm for 15 minutes, allow to stand for 1 hour.	GC/MS	NR	NR	Kage et al. 1998
Brain, liver, and kidney tissue (mouse)	Weigh sample; homogenize in aqueous zinc acetate using a rotostator at 18,000 rpm for 20 seconds; dilute with borate buffer; convert to methylene blue.	Ion-interaction reversed-phase HPLC	nmol/g	NR	Mitchell et al. 1993

Table 7-1. Analytical Methods for Determining Hydrogen Sulfide, Sulfide, and Thiosulfate in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Brain tissue (rat and human)	Homogenization in cold 0.01 M NaOH. Centrifuge and resuspend pellet; add zinc acetate and ascorbic acid; readjust pH; use continuous flow gas dialysis system to separate sulfide.	Gas dialysis/ion chromato-graphy with ECD	0.02 µg/g	95–99 (rat tissue)	Goodwin et al. 1989

[a]Conversion factor: 1 ppm=1.40 mg/m^3

ECD = electron capture detector; FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; ISE = ion-selective electrode; LC = liquid chromatography; M = molar; MS = mass spectrometry; NaOH = sodium hydroxide; NR = not reported; PFBBr = pentafluorobenzyl bromide; rpm = revolutions per minute; TBB = 1,3,5-tribromobenzene

$$Ka_1 = \frac{[HS^-(aq)][H^+(aq)]}{[H_2S(aq)]}$$

$$Ka_2 = \frac{[S^{2-}(aq)][H^+(aq)]}{[HS^-(aq)]}$$

Puacz et al. (1995) developed a catalytic method (based on the iodine-azide reaction) for the determination of sulfide in whole human blood. The method involves the generation of hydrogen sulfide in an evolution-absorption apparatus. In addition, the method allows for the determination of sulfide in blood without interference from other sulfur compounds in blood. This method is appropriate for the determination of sulfide in the concentration range of 4–3,000 µg/L. A percent recovery of 98–102% was achieved. Although the accuracy and precision of the catalytic method are comparable to those of the ion-selective electrode method, the catalytic method is simpler, faster, and would be advantageous in serial analysis.

Richardson et al. (2000) developed a method for measuring sulfide in whole blood and feces, which overcomes the problems of viscosity and turbidity that are typical for these types of samples. Turbidity of the sample interferes with colorimetric assays such as methylene blue. In this method, samples are first treated with zinc acetate to trap the sulfide as an insoluble zinc complex. Next, a microdistillation pretreatment is used to release the complexed sulfide into a sodium hydroxide solution. This microdistillation step is coupled to ion chromatography with electron capture detection. A detection limit of 2.5 µmol/L (80 µg/L) and percent recoveries of 92–102% (feces) and 79–102% (blood) were reported.

GC/FPD was employed for measuring hydrogen sulfide in human mouth air with a detection limit of 7 ppb (Blanchette and Cooper 1976) and included improvements such as calibration of the system with permeation tubes, use of a variable beam splitter to produce a wide range of vapor concentrations, and the ability to handle samples of limited volume.

For occupational measurements of airborne concentrations, NIOSH (1977a) recommended the use of a midget impinger for sampling breathing zone air and the methylene blue/spectrophotometric method for the analysis of hydrogen sulfide. The detection limit was 0.14 ppb.

GC/FID has been used for quantifying sulfur volatiles such as hydrogen sulfide in human saliva (Solis and Volpe 1973). This method included microcoulometric titrations and a procedure for incubation of saliva and sampling of headspace sulfur volatile components. The amount of total sulfur volatiles detected in control samples of saliva incubated at 37°C for 24 hours ranged from 4.55 to 13.13 ppm.

Fresh and frozen mouse tissue samples obtained from brain, liver, and kidney have been analyzed for hydrogen sulfide levels by sulfide-derived methylene blue determination using ion-interaction reversed-phase HPLC (Mitchell et al. 1993). This method can quantify nmol/g levels of sulfide. Gas dialysis/ion chromatography with ECD has been utilized for measurement of sulfide in rat brain tissue with 95–99% recovery (Goodwin et al. 1989). Goodwin et al. (1989) also applied this method to human brain tissue samples from two suspected hydrogen sulfide fatalities.

Carbonyl Sulfide. As carbonyl sulfide is believed to metabolize to hydrogen sulfide (Chengelis and Neal 1979), a limited number of tests were found for measuring carbonyl sulfide in biological samples. The following describes potential methods of identifying carbonyl sulfide in blood and breath samples. Analytical methods for biological media are presented in Table 7-2.

In blood samples, carbonyl sulfide can be detected using GC. Blood samples were obtained in heparinized or ethylenediaminetetraacetic acid (EDTA)-impregnated blood tubes, which were used to prevent clotting of the blood. Volatiles were then captured by cryogenic trapping and preconcentration on Tenax GC columns and analyzed by GC fitted with a Chrompack flame-photometric detector (Tangerman 1995).

Wang and Sahay (2009) reviewed several optical spectroscopic techniques that could be employed to detect carbonyl sulfide and other trace gasses in human breath. Cavity leak-out spectroscopy (CALOS) was used in the mid-infrared (MIR) region with a continuous wave CO_2 laser operating at 4.9 µm to detect carbonyl sulfide in breath and the ambient atmosphere. Detection limits of 9 and 7 ppt were reported for breath and atmosphere samples, respectively. Carbonyl sulfide was identified in breath samples using infrared spectroscopy and a Herriott cell with an effective path-length of 36 m. A Herriott cell is a multipass absorption cell that is commonly employed to measure low concentration components or samples that have low absorption in a spectral region. In the spectral range of 4.85–4.87 µm, a detection limit of 1.2 ppb was attained for carbonyl sulfide. A compact sensor which used a thermo-electrically cooled quantum cascade diode laser (QCDL) source operating at 4.86 µm was shown to be a

Table 7-2. Analytical Methods for Determining Carbonyl Sulfide in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Blood	Blood sampled in heparinized or EDTA-impregnated blood tubes followed by cryogenic trapping of volatiles on Tenax GC column	GC with flame-photometric detector		No data	Tangerman 1995
Breath	Direct sampling	Laser spectroscopy; continuous-wave CO_2 laser in MIR region	9 ppt	No data	Wang and Sahay 2009
Breath	Direct sampling	Laser spectroscopy using Herriott cell; spectral range of 4.85–4.87 µm	1.2 ppb	No data	Wang and Sahay 2009
Breath	Direct sampling	TDLAS-based compact absorption spectrometer with thermo-electrically cooled MIR tunable QCDL	30 ppb	No data	Wang and Sahay 2009

[a]Conversion factor: 1 ppm = 2.44 mg/m^3.

EDTA = ethylenediaminetetraacetic acid; GC = gas chromatography; MIR = mid-infrared; QCDL = quantum cascade diode laser; TDLAS = tunable diode laser absorption spectroscopy.

potentially useful sensor for measuring trace gasses in breath samples. A 30 ppb detection limit was reported for carbonyl sulfide.

7.2 ENVIRONMENTAL SAMPLES

The methods most commonly used to detect hydrogen sulfide in environmental samples include GC/FPD, gas chromatography with electron capture detection (GC/ECD), iodometric methods, the methylene blue colorimetric or spectrophotometric method, the spot method using paper or tiles impregnated with lead acetate or mercuric chloride, ion chromatography with conductivity, and potentiometric titration with a sulfide ion-selective electrode. Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-3.

Hydrogen Sulfide. Several methods for determining hydrogen sulfide in air have been investigated. GC/FPD has been widely used for analyses of hydrogen sulfide at levels ranging from 10^{-11} to 10^{-8} g/ 0.56 mL (EPA 1978; Stetter et al. 1977) and for hydrogen sulfide in emissions from tail gas controls units of sulfur recovery plants to a sensitivity of 0.5 ppmv (EPA 2000b). Sampling of a standard reference (0.055 ppm hydrogen sulfide) with this method resulted in a relative standard deviation of <3% (WHO 1981). The sensitivity of hydrogen sulfide detection in air was improved with GC/ECD (Stetter et al. 1977). The detector operation is based upon the measurement of the current when hydrogen sulfide is electrochemically oxidized at a diffusion electrode. Use of this method resulted in a lower detection limit of $3x10^{-12}$ g hydrogen sulfide and a precision of 0.5%. Analyses were achieved within 2 minutes. GC/FPD has been used to measure hydrogen sulfide that has been removed from air by activated carbon fiber (Choi et al. 1991). Activated carbon fiber (made from coal tar) effectively oxidized hydrogen sulfide (200 ppm) to sulfate.

Methylene blue techniques have been widely utilized for continuous, quantitative monitoring of hydrogen sulfide in air and are sensitive to hydrogen sulfide concentrations down to approximately 1–3 ppb (NIOSH 1977a). This method provides adequate specificity with good accuracy and precision (WHO 1981). The amount of sulfide is determined by spectrophotometric or colorimetric measurement of methylene blue. The method has been improved to eliminate the formation of the precipitate cadmium sulfide, which can result in the obstruction of the sampling impinger (Van Den Berge et al. 1985). The simplified method can also be used to measure hydrogen sulfide levels in the viscose rayon industry because it is not as sensitive to carbon disulfide. Limitations of the methylene blue method include potential interferences from light, mercaptans, sulfides, nitrogen dioxide, and sulfur dioxide, and that the

Table 7-3. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Filter through a 0.5 µm Zefluor; absorb on a solid sorbent tube containing shell charcoal; desorb with ammonia hydroxide and hydrogen peroxide; dilute.	Ion chromato-graphy, conductivity	11 µg/sample; working range 0.6–14 ppm for a 20-L air sample	NR	NIOSH 1994b (Method 6013)
Air	Aspirate through cadmium hydroxide; precipitate as cadmium sulfide; add STRactan 10®; react with N,N-dimethyl-p-phenylene-diamine and ferric chloride to yield methylene blue.	Spectro-photometry	0.20 µg/m^3	80	Adams et al. 1975; EPA 1978; NIOSH 1977a
Air	Aspirate through sodium hydroxide and ethanol; react with N,N-dimethyl-p-pheny-lenediamine and ferric chloride to yield methylene blue.	Spectro-photometry	No data	NR	Van den Berge et al. 1985
Air	Absorb onto cadmium(II)-exchange zeolite; precipitate as cadmium sulfide; convert to methylene blue; measure at 750 nm.	PAS	0.01 µg	NR	NIOSH 1979
Air	Electrochemically oxidize sample at potential-controlled Teflon-bonded diffusion electrode.	GC/ECD	3 pg	NR	Stetter et al. 1977
Air	Introduce sampled air and carrier gas onto column.	GC/FPD	5–13 µg/m^3	NR	EPA 1978
Air	Introduce sample onto column packed with activated carbon filter.	GC/FPD	No data	NR	Choi et al. 1991
Air	Absorb in an impinger containing a standardized solution of iodine and potassium iodide; titrate with standard sodium thiosulfate solution.	Iodometric titration	No data	NR	EPA 1978
Air	Trap H_2S in aqueous NaOH and ascorbic acid in a midget impinger; titrate resulting sulfide ion with $CdSO_4$ solution.	Potentiometry	ppb levels	NR	Ehman 1976

Table 7-3. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Air	Aspirate through ammoniacal cadmium chloride; strip sulfur dioxide by aeration; dissolve cadmium sulfide; precipitate in concentrated HCl; titrate with iodine using a starch indicator.	Iodometric titration	0.7 µg/L	NR	EPA 1978
Air	Filter measured volume of air through lead-acetate-impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Lead-acetate-impregnated filter paper tape	No data	NR	EPA 1978
Air	Filter measured volume of air through mercuric chloride-impregnated filter paper tape; compare optical density with unexposed impregnated spot of similar area.	Mercuric chloride-impregnated filter paper tape	0.7 µg/m^3 (0.5 ppb)	NR	EPA 1978
Air	Pass air through silver membrane filter.	Silver membrane filters/optical density measurements	No data	NR	EPA 1978
Air (fuel gas streams in petroleum refineries)	Hydrogen sulfide is absorbed on impingers containing cadmium sulfate, forming cadmium sulfide, which is measured iodometrically.	Iodometric titration	8–740 mg/m^3 (6–520 ppm)	NR	EPA 2000a
Air (emissions from stationary sources)	A gas sample is extracted from the emission source and diluted with clean dry air.	GC/FPD	0.5 ppmv	NR	EPA 2000b
Water	Add an amine-sulfuric acid reagent and a ferric chloride solution to the sample, mix gently; after 3–5 minutes add $(NH_4)_2HPO_4$ solution; analyze after 3–15 minutes.	Colorimetry	Applicable to sulfide concentrations ranging from 0.1 to 20.0 mg/L	89–92	APHA 1998 (Methylene Blue Method)
Water	For unpreserved samples, add solutions of zinc acetate, sodium hydroxide, and ascorbic acid, shake and let stand for 30 minutes; for preserved samples, omit the zinc acetate step.	Spectro-photometry	Applicable at sulfide concentrations from 0.002 to 0.100 mg/L	97.6–104.2	APHA 1998 (Gas Dialysis, Automated Methylene Blue Method)

Table 7-3. Analytical Methods for Determining Hydrogen Sulfide and Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit[a]	Percent recovery	Reference
Water	To the sample, add an excess of standard iodine solution; back titrate with a sodium thiosulfate solution.	Iodometric titration	Accurate method for determining sulfide concentrations >1 mg/L	NR	APHA 1998 (Iodometric Method)
Water	Add an AAR and zinc acetate to the sample; measure the potential and compare to a calibration curve.	ISE	Applicable for sulfide concentrations >0.03 mg/L	NR	APHA 1998 (ISE Method)
Water	Collect water sample; acidify; strip sample with helium; collect gas in nitrogen-cooled trap.	GC/FPD	0.6 pmol/L	NR	Radford-Knoery and Cutter 1993
Water and sludge	Acidify sample to convert sulfide ion to hydrogen sulfide; measure hydrogen sulfide absorption at 196 nm using the selenium atomic line.	AAS	0.25 µg (1–10 mL sample volume)	NR	Parvinen and Lajunen 1994
Sediment	Acidify sample to convert sulfide ion to hydrogen sulfide; trap hydrogen sulfide in sodium hydroxide; sulfide reacts with N,N-dimethyl-p-phenylene-diamine to form methylene blue.	Colorimetry	0.01 µmol/g	NR	Allen et al. 1994
Sediment	Trap in silver nitrate solution as insoluble silver sulfide.	Gravimetry	10 µmol/g	NR	Allen et al. 1994
Sediment	Trap in a sulfide antioxidant buffer.	Potentiometry/ ISE	No data	NR	Allen et al. 1994

[a]Conversion factor: 1 ppm=1.40 mg/m^3

AAR = alkaline antioxidant reagent; AAS = atomic absorption spectroscopy; $CdSO_4$ = cadmium sulfate; ECD = electron capture detector; FPD = flame photometric detection; GC = gas chromatography; HCl = hydrochloric acid; H_2S = hydrogen sulfide; ISE = ion-selective electrode; NaOH = sodium hydroxide; NR = not reported; PAS = photoacoustic spectroscopy

system is not portable (NIOSH 1977a). Photoacoustic spectroscopy of hydrogen sulfide converted to methylene blue has been demonstrated to yield greater sensitivity than standard spectrophotometric methods (NIOSH 1979). By maximizing instrument response to the 750-nm peak, it was possible to achieve a detection limit of 0.01 μg when collected at 2.0 L/minute for a 1-hour period.

NIOSH (Method 6013) describes the measurement of hydrogen sulfide in the air by ion chromatography (NIOSH 1994b). This method has a working range of 0.6–14 ppm for a 20-L air sample and an estimated limit of detection of 11 μg per sample. However, sulfur dioxide may interfere with the measurement of hydrogen sulfide.

The iodometric method has been utilized in analyzing hydrogen sulfide in the air (EPA 1978). The method is based on the oxidation of hydrogen sulfide by absorption of the gas sample in an impinger containing a standardized solution of iodine and potassium iodide. This solution will also oxidize sulfur dioxide. The iodometric method is suitable for occupational settings. The accuracy of the method is approximately 0.50 ppm hydrogen sulfide for a 30-L air sample (EPA 1978). Another application of the iodometric method is for the determination of hydrogen sulfide in fuel gas emissions in petroleum refineries (EPA 2000a). In this method, the sample is extracted from a source and passed through a series of impingers containing cadmium sulfate. The hydrogen sulfide is absorbed, forming cadmium sulfide, which is then measured iodometrically. The sensitivity range of this method is 8–740 mg/m^3 (6–520 ppm) (EPA 2000a).

Paper tapes impregnated with lead acetate have been widely used for air sample measurements of hydrogen sulfide in the field (EPA 1978; WHO 1981). The presence of other substances capable of oxidizing lead sulfide can lead to errors. This method has been improved by impregnating the paper with mercuric chloride or silver nitrate (EPA 1978; WHO 1981). Mercuric chloride paper tape is sensitive and reliable for measurement of hydrogen sulfide in air with a sensitivity of 0.7 μg/L (EPA 1978). Tapes impregnated with silver nitrate are suitable for determination of hydrogen sulfide concentrations in the range of 0.001–50 ppm (WHO 1981).

Potentiometric titration with a sulfide ion-selective electrode as an indicator has been used to measure hydrogen sulfide in the air at ppb levels (Ehman 1976). This method has been shown to have very good accuracy and precision. No interference could be found from nitrogen dioxide, sulfur dioxide, or ozone.

Passive card monitors can be used to detect hydrogen sulfide in workplace environments (Saunders et al. 2002). These monitors can be categorized as quantitative, semiquantitative, and indicator cards. Quantitative cards use an optical reader to assess exposure and calculate a hydrogen sulfide concentration in air; the results are digitally displayed. Semiquantitative cards are read by comparing the exposed card to a chart or by observing a progressive color development in windows on the card that represent differing exposure concentration ranges. The indicator cards change color above a certain threshold concentration of hydrogen sulfide. Saunders et al. (2002) reported detection limits of 4–8 and 0.8–4 ppm-hours for two commercial quantitative card monitors, 1 and 0.1 ppm-hours for two commercial semiquantitative card monitors, and 0.05 and 0.4 ppm-hour for two commercial indicator card monitors.

Badges that can be worn in a worker's, breathing zone that change color based on exposure to toxic gases (including hydrogen sulfide) are available from American Gas & Chemical Co. The sensitivity for the hydrogen sulfide badges is 10 ppm/10 minutes with a color change from white to brown (American Gas & Chemical Co. 2005; Ho et al. 2001). Other colorimetric methods for monitoring of hydrogen sulfide include handheld colorimetric tubes. Air is drawn through the tube and a color change indicates the presence of hydrogen sulfide by reaction with a chemical reagent in the glass tube. Tubes for hydrogen sulfide are available from Draeger Safety, Inc. in various measuring ranges from 0–5 to 100–2,000 ppm (Draeger Safety 2005).

Electrochemical sensors are the most commonly used sensors for toxic gases (including hydrogen sulfide) and are the best sensor for ambient toxic gas monitoring. These sensors are specific to a particular gas, are very accurate, do not get poisoned, and monitor at the ppm level. However, they have a narrow temperature range and a short shelf life, particularly in very hot and dry areas. When sensitivity to low concentrations of hydrogen sulfide (ppm levels) is needed, semiconductor sensors are one of the best sensors. Some advantages of semiconductor sensors for hydrogen sulfide include small size, ruggedness, and sensitivity to ppm concentrations. Disadvantages include slow response on aged sensors, requirement of a temperature controlled heater, and cost (Delphian Corporation 2005).

The Iowa Department of Natural Resources (DNR) monitors airborne levels of ammonia, hydrogen sulfide, and odor concentrations near animal feeding operations. Approved monitoring methods and equipment for the hydrogen sulfide must incorporate a thermal oxidizer and an EPA reference method analyzer that is designed for sulfur dioxide. There are several instruments that meet the requirements for the Iowa DNR, all of which detect hydrogen sulfide by first oxidizing it to sulfur dioxide, which is then measured using a fluorescence detector. The hydrogen sulfide and total reduced sulfide analyzer (Model

101A) from Advanced Pollution Instrumentation, Inc. has a range of 0–50 ppb to 0–2 ppm for hydrogen sulfide. In addition, three hydrogen sulfide analyzers from Thermo Electron Corporation are also approved by the Iowa DNR. Minimum detection limits of 0.5 ppb can be achieved for models 45C and 450C and 0.06 ppb can be achieved for model 450C-TL (API 2005; Iowa DNR 2004, 2005; Thermo Electron Corp. 2005a, 2005b, 2005c).

The APHA (1998) defines three categories of sulfides that must be taken into account for analytical methods measuring sulfides in water: total sulfide, dissolved sulfide, and un-ionized hydrogen sulfide. Total sulfide includes all sulfide containing species, dissolved hydrogen sulfide, bisulfide ion, and acid-soluble metal sulfides in suspended matter. Dissolved sulfide includes sulfide-containing components that remain after suspended solids have been removed. The concentration of the un-ionized hydrogen sulfide can be calculated from the concentration of dissolved sulfide components, pH of the solution, and the acidity constants for hydrogen sulfide using the equilibrium expressions for the ionization of hydrogen sulfide and bisulfide ion (APHA 1998).

Samples that contain sulfide species can be either analyzed immediately after collection, or preserved with a zinc acetate solution for later analysis (APHA 1998). The addition of zinc ion (Zn^{2+}) to the sample will precipitate any sulfides as zinc sulfide. A qualitative sulfide test (such as a precipitation test using potassium antimony tartrate or testing for hydrogen sulfide vapors using lead acetate paper or silver foil) can be useful and are advisable when testing industrial wastes that may contain substances that interfere with certain test methods, such as the methylene blue method (APHA 1998).

The total sulfide concentration in a water sample can be determined using an iodometric titration. In this method, sulfide is reacted with a measured excess of iodine in an acidic solution; the remaining unreacted iodine is then determined by titration with a thiosulfate solution. This method is an accurate method for determining sulfide concentrations of >1 mg/L, if interferences are absent and the loss of hydrogen sulfide from the solution is avoided. The iodometric method is best suited for the analysis of samples freshly taken (i.e., from wells and springs) (APHA 1998).

The methylene blue method is applicable to sulfide concentrations ranging from 0.1 to 20.0 mg/L. In this method, an amine-sulfuric acid reagent and a ferric chloride solution are added to the sample to produce methylene blue, which is then quantified colorimetrically. In the automated methylene blue method, a gas dialysis technique separates the sulfide from the sample matrix, which removes most inferences (i.e.,

turbidity and color). Addition of ascorbic acid, an antioxidant, improves sulfide recovery. The automated methylene blue method is applicable at sulfide concentrations from 0.002 to 0.100 mg/L (APHA 1998).

Potentiometric methods using a silver electrode are also suitable for determination of sulfide concentrations in water and are unaffected by sample color or turbidly. In this method, an alkaline antioxidant reagent (AAR) and zinc acetate are added to the sample. The potential of the sample is measured using an ISE and the measurement is compared to a calibration curve. This method is applicable for sulfide concentrations >0.03 mg/L (APHA 1998).

Three methods for quantifying acid volatile sulfides in sediment have been described (Allen et al. 1994). These include methylene blue/colorimetric methods, gravimetry, and potentiometry with an ion-selective electrode. Prior to measurement, the acid volatile sulfide in the sample is converted to hydrogen sulfide by acidification. The hydrogen sulfide is then purged from the sample and trapped in aqueous solution for the colorimetric and potentiometric methods. In the gravimetric method, hydrogen sulfide is trapped with silver nitrate ($AgNO_3$), and the mass of the insoluble silver sulfide (Ag_2S) that is formed is determined. The methylene blue/colorimetric method is generally preferred and is capable of determining acid volatile sulfide concentrations in sediment as low as 0.01 μmol/g (0.3 μg/g) dry weight. The gravimetric method can be used for samples with moderate or high acid volatile sulfides. However, below concentrations of acid volatile sulfides in dry sediment of 10 μmol/g (320 μg/g), accuracy may be affected by incomplete recovery of precipitate or by weighing errors. The limit of detection of the ion-selective electrode method as applied to measuring hydrogen disulfide in sediment was not reported.

GC/FPD has been used to measure hydrogen sulfide, free (uncomplexed) sulfide, and dissolved metal sulfide complexes in water (Radford-Knoery and Cutter 1993). Hydrogen sulfide was measured in the headspace of the sample (100 mL) with a detection limit of 0.6 pmol/L (20 pg/L). A detection limit of 0.2 pmol/L (6 pg/L) was obtained for total dissolved sulfide. This method allows for the determination of the concentration of free sulfide that is in equilibrium with hydrogen sulfide. Complexed sulfide can be estimated from the difference between total dissolved sulfide and free sulfide.

A molecular absorption spectrophotometry method using a sharp-line irradiation source has been developed for the determination of sulfide (as hydrogen sulfide) in water and sludge samples. The method was tested with measurements of real waste water samples. The limit of detection was 0.25 μg (1–10 mL sample volume) (Parvinen and Lajunen 1994).

Carbonyl Sulfide. Carbonyl sulfide can be detected in environmental samples using various gas chromatography methods, as well as cell-based sensors. Details of commonly used analytical methods to detect carbonyl sulfide in several types of environmental samples are presented in Table 7-4. Air concentrations of carbonyl sulfide can be determined using gas chromatography. Sulfur compounds are collected in a small glass tube that is packed with Tenax GC, and concentrated at -196°C. Water is removed from the air samples using calcium chloride. The Tenax tube is placed in the GC, where sulfur compounds are released at 200°C into a carrier gas stream and analyzed using a flame photometric detector. After 1 week of storage at -196°C, 91% of carbonyl sulfide was recovered (Tangerman 1986).

Blake et al. (2004) also determined carbonyl sulfide concentrations in the atmosphere utilizing a mass spectrometer method. From an aircraft, whole air samples were collected using an external air intake to fill 2 L stainless steel canisters to approximately 4 atmospheres of pressure. Samples were pre-concentrated at liquid nitrogen temperatures (-196°C) on a stainless steel loop filled with glass beads, which was then put in hot water to evaporate the sample. The sample was flushed to a splitter, where it broke into five streams and went to one of five column-detector combinations. Concentrations were determined using a DB-5ms column with an HP-5973 quadrupole Mass Spectrometric Detector, which was used in single ion monitoring (SIM) mode. Carbonyl sulfide was measured with a detection limit of 20 pptv (Blake et al. 2004).

The NASA Chemical Instrumentation Test and Evaluation 3 (CITE 3) method evaluates carbonyl sulfide concentrations in air. The method utilizes a gas chromatograph/mass spectrometer (GC/MS) and an isotopically labeled compound as an internal standard (GC/MS/ILS). GC/MS/ILS uses an isotopomer of the analyte to calibrate every sample. The detection limit of this method has been reported as 4 fmol/s (Bandy et al. 1993).

Oceanic air samples have been analyzed for carbonyl sulfide. Samples were collected in 6- and 800-mL stainless steel bottles using a Metal Bellows MB-155 pump to fill to an internal pressure of 30 psi. Samples in 35- and 1.6-L bottles were collected cryogenically (which increases stability) by putting the canister on liquid nitrogen and utilizing the internal vacuum to collect the sample. The samples were analyzed using a Finnigan 4021 GC/MS data system (Rasmussen et al. 1982a).

Carbonyl sulfide can also be monitored in air using a pyrolyzer-electrochemical cell-based sensor, such as the MIDAS gas detector. The system utilizes an internal pump to sample the air, which is then fed to a pyrolyzer. It converts carbonyl sulfide to hydrogen sulfide by pyrolysis at high temperatures and in

Table 7-4. Analytical Methods for Determining Carbonyl Sulfide in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Whole air samples from aircraft; preconcentrated at -196°C, followed by hot water evaporation and split into five streams.	MS in SIM mode	20 pptv		Blake et al. 2004
Air	Collected in glass tube with Tenax GC; concentrated at -196°C; water removed with calcium chloride.	GC with flame photometric detector		91%	Tangerman 1986
Air	Air sample.	GC/MS/ILS	4 fmol/s		Bandy et al. 1993
Air	Internal pump to sample air; pyrolyze carbonyl sulfide to hydrogen sulfide at ambient moisture.	Pyrolyzer-electrochemical cell-based sensor	20 ppm		Chase et al. 2010
Air	Collected in steel bottles with pump or cryogenically.	GC/MS data system			Rasmussen et al. 1982a
Seawater	Air samples equilibrated with seawater; separated on chromatographic column.	Flame photometric sulfur detector			Meinrat et al. 1992
Seawater	Collected in vacuum extraction flasks; air removed.	GC/MS data system			Rasmussen et al. 1982a

GC = gas chromatography; GC/MS/ILS = gas chromatography/mass spectrometry with isotopically labeled compound as internal standard; MS = mass spectrometry; SIM = single ion monitoring

ambient moisture. An electrochemical sensor cartridge is then used to determine the hydrogen sulfide content. The limit of detection for carbonyl sulfide was reported as 20 ppm (Chase et al. 2010).

The optical sensors reviewed by Wang and Sahay (2009) and discussed in Section 7.1 for potential use in exhaled breath analysis could also be employed to analyze for carbonyl sulfide in ambient air.

The concentration of dissolved carbonyl sulfide in seawater can be determined by equilibrating air samples with seawater. The equilibrated air samples are then sent through a cold trap that is submerged in liquid nitrogen. Trace gases are then separated on a chromatographic column and the carbonyl sulfide saturation ratio is determined using a flame photometric sulfur detector. The dissolved carbonyl sulfide concentration is calculated from the saturation ratio using Henry's law (Meinrat et al. 1992).

In another study, samples of seawater were obtained using 1,000 mL vacuum extraction flasks, constructed of Erlenmeyer flasks with a Kovar-to-glass seal on the top connected to a valve. Bottles were filled such that the headspace air and water sample were in equal volumes. The flask was placed in a heated chamber at 100°C and the air was pumped out with a vacuum for one hour to keep a pressure of 0.1 torr. The sample was then collected by submerging the flask and releasing the valve or by removing the sample under vacuum by putting the water sample in a funnel and opening the valve. The samples were analyzed using a Finnigan 4021 GC/MS data system and the concentration of carbonyl sulfide was calculated using Henry's law and the headspace concentration (Rasmussen et al. 1982a).

7.3 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 and carbonyl sulfide is available. Where adequate information is not available, ATSDR, in conjunction with 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 and carbonyl 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.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods are available for measuring hydrogen sulfide in expired air (Blanchette and Cooper 1976; NIOSH 1977a). Methods are available for measuring sulfide in blood (Puacz et al. 1995; Richardson et al. 2000) and brain tissue (Goodwin et al. 1989) and for measuring sulfur volatiles in saliva (Solis and Volpe 1973). Methods are available for measuring thiosulfate levels in urine (Kage et al. 1992; Kangas and Savolainen 1987; Milby and Baselt 1999). Analytical methods with satisfactory sensitivity and precision are available to determine levels of hydrogen sulfide and thiosulfate in human tissues and body fluids. Methods that can quantitatively correlate levels in biological fluids and tissues with environmental exposure levels would be useful in estimating exposure to hydrogen sulfide. Limited methods are available for determining carbonyl sulfide concentrations in biological samples (Tangerman 1995; Wang and Sahay 2009) since it is likely that carbonyl sulfide metabolizes to hydrogen sulfide in biological organisms.

Effect. No methods have been identified that can be used to directly associate levels of hydrogen sulfide in biological samples with the onset of adverse health effects.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods are available for measuring hydrogen sulfide in air (Ehman 1976; EPA 1978, 2000a, 2000b; NIOSH 1977a, 1979, 1994b; Stetter et al. 1977; Van Den Berge et al. 1985; WHO 1981). Methods are available for measuring sulfide in sediment (Allen et al. 1994), water (APHA 1998; Radford-Knoery and Cutter 1993), and sludge (Parvinen and Lajunen 1994). Ho et al. (2001) reviewed sensors and technologies that can be used to monitor various chemicals (including hydrogen sulfide) with particular attention to sensors that have the potential to be used for long-term monitoring applications. Since hydrogen sulfide is part of the natural environment, dissociates in aqueous solution, and can bind to various metal ions in environmental media, in most cases, it would not be possible to distinguish the specific source of sulfide ions in environmental media. In the event of a release of hydrogen sulfide, increased sulfide concentrations in surrounding environmental media would likely be due to the release.

7.3.2 Ongoing Studies

No ongoing studies for examining analytical methods to detect hydrogen sulfide or carbonyl sulfide levels were identified.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates intended to serve as screening levels used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An acute-duration inhalation MRL of 0.07 ppm was derived for hydrogen sulfide. This MRL is based on a minimal LOAEL of 2 ppm for a >30% alteration in two measures of lung function that are suggestive of bronchial obstruction (airway resistance and specific airway conductance) in 2 out of 10 persons with asthma (Jappinen et al. 1990). The MRL was derived by dividing the unadjusted LOAEL by an uncertainty factor of 27 (3 for the use of a minimal LOAEL, 3 for human variability, and 3 for database deficiencies). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

An intermediate-duration inhalation MRL of 0.02 ppm was derived for hydrogen sulfide. This MRL is based on a NOAEL of 10 ppm and a LOAEL of 30 ppm for olfactory neuron loss in rats exposed to hydrogen sulfide 6 hours/day, 7 days/week for 10 weeks (Brenneman et al. 2000). The MRL was derived by dividing the human equivalent concentration of the NOAEL by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability). Further details on the derivation of this MRL can be found in the MRL worksheets in Appendix A of this profile.

EPA has derived a chronic inhalation reference concentration (RfC) for chronic exposure to hydrogen sulfide. The RfC of 0.002 mg/m^3 (0.001 ppm) is based on a NOAEL of 13.9 mg/m^3 (10 ppm) and a LOAEL of 41.7 mg/m^3 (30 ppm) for nasal lesions of the olfactory mucosa in rats (Brenneman et al. 2000). The $NOAEL_{HEC}$ of 0.64 mg/m^3 was divided by an uncertainty factor of 300 (3 for interspecies extrapolation with dosimetric adjustment from rat to human, 10 for sensitive populations, and 10 for subchronic exposure) (IRIS 2003).

EPA has not derived an oral reference dose (RfD) or an inhalation RfC for chronic exposure to carbonyl sulfide (IRIS 2002).

EPA has designated hydrogen sulfide and carbonyl sulfide as hazardous air pollutants (HAPs) under the Clean Air Act (CAA) (EPA 2009d). Hydrogen sulfide and carbonyl sulfide are on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-

to-Know Act of 1986" and have been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2012f). The RQ represents the amount of a designated hazardous substance that, when released to the environment, must be reported to the appropriate authority.

The international and national regulations, advisories, and guidelines regarding hydrogen sulfide and carbonyl sulfide in air, water, and other media are summarized in Tables 8-1 and 8-2.

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data[a]	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	1 ppm	ACGIH 2012b
	STEL	5 ppm	
AIHA	ERPG-1[b,c]	0.1 ppm	AIHA 2011
	ERPG-2	30 ppm	
	ERPG-3	100 ppm	
DOE	PAC-1[d]	0.51 ppm	DOE 2012
	PAC-2	27 ppm	
	PAC-3	50 ppm	
EPA	AEGL-1[e]		EPA 2013a
	10-minutes	0.75 ppm	
	30-minutes	0.60 ppm	
	60-minutes	0.51 ppm	
	4-hours	0.36 ppm	
	8-hours	0.33 ppm	
	AEGL-2		
	10-minutes	41 ppm	
	30-minutes	32 ppm	
	60-minutes	27 ppm	
	4-hours	20 ppm	
	8-hours	17 ppm	
	AEGL-3		
	10-minutes	76 ppm	
	30-minutes	59 ppm	
	60-minutes	50 ppm	
	4-hours	37 ppm	
	8-hours	31 ppm	
	Hazardous air pollutant	Yes	EPA 2009d 42 USC 7412
	NAAQS	No data	EPA 2013d

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
NIOSH	REL (10-minute ceiling)	10 ppm	NIOSH 2011
	IDLH	100 ppm	
NATIONAL *(cont.)*			
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013b 29 CFR 1910.1000, Table Z-2
	Acceptable ceiling concentration	20 ppm	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift	50 ppm for 10 minutes once only if no other measured exposure occurs	
	Highly hazardous chemicals (threshold quantity)	1,500 pounds	OSHA 2013a 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2012c 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012d
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria		EPA 2009c
	Freshwater (criterion continuous concentration)	2.0 µg/L	
	Saltwater (criterion continuous concentration)	2.0 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	100 pounds	EPA 2012a 40 CFR 117.3
c. Food			
FDA	EAFUS[f]	Yes	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2012b
EPA	Carcinogenicity classification	Data inadequate for assessment	IRIS 2003
	RfC	$2x10^{-3}$ mg/m^3	
	RfD	No data	
	Identification and listing of hazardous waste	U135	EPA 2012b 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	No data	EPA 2013c

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference
	Master Testing List	No data	EPA 2013a
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998b 63 FR 60332
NATIONAL *(cont.)*			
EPA	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2012e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity pursuant to Section 311(b)(2) of the Clean Water Act and Section 3001 of RCRA	100 pounds	EPA 2012f 40 CFR 302.4
	Effective date of toxic chemical release reporting	01/01/1994	EPA 2012g 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity[g]		EPA 2012h 40 CFR 355, Appendix A
	Reportable quantity	100 pounds	
	Threshold planning quantity	500 pounds	
	TSCA chemical lists and reporting periods	No data	EPA 2012i 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2012j 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011

[a]A guideline value was not established for hydrogen sulfide because it occurs in drinking-water at concentrations well below those of health concern; although it may affect acceptability of drinking water (WHO 2011).
[b]ERPG-1: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined, objectionable odor; ERPG-2: maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action; ERPG-3: is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 hour without experiencing or developing life-threatening health effects (AIHA 2011).
[c]Odor should be detectable near ERPG-1.
[d]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[e]AEGL-1: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects; however, these effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape; AEGL-3: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death (EPA 2013a).
[f]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[g]Hydrogen sulfide does not meet the toxicity criteria but because of its acute lethality, high production volume, or known risk it is considered a chemical of concern.

Table 8-1. Regulations and Guidelines Applicable to Hydrogen Sulfide

Agency	Description	Information	Reference

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure level; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

Table 8-2. Regulations and Guidelines Applicable to Carbonyl Sulfide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	5 ppm	ACGIH 2012a
AIHA	ERPG-1, -2, -3	No data	AIHA 2011
DOE	PAC-1[a]	5 ppm	DOE 2012
	PAC-2	55 ppm	
	PAC-3	150 ppm	
EPA	AEGL-1[b]	Not recommended due to lack of warning properties	EPA 2013b
	AEGL-2		
	10-minutes	69 ppm	
	30-minutes	69 ppm	
	60-minutes	55 ppm	
	4-hours	34 ppm	
	8-hours	23 ppm	
	AEGL-3		
	10-minutes	190 ppm	
	30-minutes	190 ppm	
	60-minutes	150 ppm	
	4-hours	95 ppm	
	8-hours	48 ppm	
	Hazardous air pollutant	Yes	EPA 2009d 42 USC 7412
	NAAQS	No data	EPA 2013d
NIOSH	REL (10-hour TWA)	No data	NIOSH 2013
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013c 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A

Table 8-2. Regulations and Guidelines Applicable to Carbonyl Sulfide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2012c 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012d
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2009c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2012a 40 CFR 117.3
c. Food			
FDA	EAFUS[c]	No data	FDA 2013
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2012a
EPA	Carcinogenicity classification	No data	IRIS 2002
	RfC	No data	
	RfD	No data	
	Identification and listing of hazardous waste	No data	EPA 2012b 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	No data	EPA 2013c
	Master Testing List	Yes[d]	EPA 2013d
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998b 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2012e 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity pursuant to Section 112 of the Clean Air Act	100 pounds	EPA 2012f 40 CFR 302.4
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2012g 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2012h 40 CFR 355, Appendix A

Table 8-2. Regulations and Guidelines Applicable to Carbonyl Sulfide

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA chemical lists and reporting periods	No data	EPA 2012i 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2012j 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011

[a]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects (DOE 2012).
[b]AEGL-1: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, nonsensory effects; however, these effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape; AEGL-3: is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening adverse health effects or death (EPA 2013a).
[c]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[d]Testing action development underway for health effects including mutagenicity, acute and subchronic toxicity, neurotoxicity, developmental and reproductive toxicity, carcinogenicity and immunotoxicity.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—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.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL), prepare toxicological profiles for each substance included on the priority list of hazardous substances, and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates (which are intended to serve as screening levels) are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be greater than 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [x] Acute [ ] Intermediate [ ] Chronic
Graph Key: 17
Species: Human

Minimal Risk Level: 0.07 [ ] mg/kg/day [x] ppm

Reference: Jäppinen P, Vikka V, Marttila O, et al. 1990. Exposure to hydrogen sulphide and respiratory function. Br J Intern Med 47:824-828.

Experimental design: This study evaluated lung function in three male and seven female subjects with bronchial asthma requiring medication for 1–13 years; none of the subjects had severe asthma. The subjects were exposed to 2 ppm hydrogen sulfide for 30 minutes. Respiratory function in response to a histamine challenge was assessed prior to exposure and after exposure.

Effect noted in study and corresponding doses: No statistically significant changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and forced expiratory flow were noted. Airway resistance (Raw) and specific airway conductance (SGaw) did not show statistically significant changes when examined as a group. In two subjects, there were changes of over 30% in both Raw and SGaw; these changes were suggestive of bronchial obstruction. Additionally, 3 of 10 subjects complained of headaches after exposure.

Dose and end point used for MRL derivation:

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[x] 3 for use of a minimal LOAEL
[ ] 10 for extrapolation from animals to humans
[x] 3 for human variability
[x] 3 for database deficiencies

The 2 ppm concentration was considered a minimally adverse effect level because the changes in airway resistance and specific airway conductance were only observed in 2 of 10 subjects. Because the study was conducted using asthmatics (who are likely to be a sensitive subpopulation) a partial uncertainty factor of 3 was used to account for human variability. An additional uncertainty factor of 3 was used for database deficiencies due to concern for the short (30-minute) exposure duration in the principal study.

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: No.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Bhambhani et al. (1996b) evaluated the acute effects of hydrogen sulfide on the physiological and hematological health of male and female volunteers exposed to 5 ppm during two 30-minute sessions of submaximal exercise (50% of maximum aerobic power). No significant changes in any parameter were noted in the women, whereas the men showed a significant decrease in muscle citrate synthetase as well as nonsignificant changes in lactate, lactate dehydrogenase, and cytochome oxidase. Together, these changes were considered indicative of compromise of aerobic metabolism.

No respiratory or cardiovascular effects were observed in 16 male volunteers exposed by oral inhalation to hydrogen sulfide at 0.5, 2, or 5 ppm for >16 minutes while exercising (Bhambhani and Singh 1991). The end points examined included heart rate, oxygen uptake, carbon dioxide output, and blood gases. Airway resistance and conductance were not measured in this study. No significant changes in pulmonary function parameters were noted in individuals exposed to 10 ppm hydrogen sulfide for 15 minutes during exercise (Bhambhani et al. 1996a).

Respiratory distress was noted in two workers exposed to >40 ppm hydrogen sulfide for under 25 minutes (Spolyar 1951). In animals, impacts on the respiratory system such as increases in the cellularity and lactate dehydrogenase and alkaline phosphatase activity in bronchial lavage fluids have been seen at exposures as low as 10 ppm for 4 hours (Lopez et al. 1987), although without a dose-related trend.

Moderate to massive pulmonary edema was observed in rats exposed to 375 or 399 ppm for 4 hours (Prior et al. 1990). A significant dose-related decrease in lung microsomal cytochrome c oxidase activity was seen in rats following a 4 hour exposure to 50, 200, or 400 ppm hydrogen sulfide (Khan et al. 1990). Similarly, succinate oxidase activity also decreased in a dose-related fashion; although no affect was observed at the lowest dose. Cytochrome oxidase levels returned to normal by 24 hours postexposure in animals in the 200 ppm group, but not the 400 ppm group. Exposure at the two higher dose levels was also associated with complete abolition of the zymosan-induced stimulation of respiratory rates of pulmonary alveolar macrophages and there were significant decreases in the number of viable macrophages in lung lavage fluids at the highest dose (Khan et al. 1991).

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APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Hydrogen Sulfide
CAS Number: 7783-06-4
Date: September 2014
Profile Status: Draft for Public Comment
Route: [x] Inhalation [ ] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 41
Species: Rat

Minimal Risk Level: 0.02 [ ] mg/kg/day [x] ppm

Reference: Brenneman KA, James RA, Gross EA, et al. 2000. Olfactory neuron loss in adult male CD rats following subchronic inhalation exposure to hydrogen sulfide. Toxicol Pathol 28(2):326-333.

Experimental design: Groups of male Sprague Dawley rats (12/group) were exposed to 0, 10, 30, or 80 ppm hydrogen sulfide 6 hours/day, 7 days/week for 10 weeks. Parameters used to assess toxicity were limited to extensive histopathological examination of the nasal cavity (six transverse sections examined via light microscopy; transverse sections form a series of circumferential slices [labeled levels 1–6], which allow for a thorough evaluation of all major structures and mucosae of the nasal cavity).

Effect noted in study and corresponding doses: 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. The severity of the olfactory lesions was scored as 1 mild, 2 moderate, or 3 severe. For the olfactory neuron loss, the mild, moderate, or severe severity scores corresponded to 26–50, 51–75, and 76–100%, respectively, reduction in the normal thickness of the olfactory neuron layer. For the basal cell hyperplasia, mild, moderate, or severe severity scores corresponded to 1–33, 34–67, or 68–100% of the normal thickness of the olfactory neuron cell layer replaced by basal cells. No olfactory lesions were observed in the controls or rats exposed to 10 ppm. At 30 ppm, olfactory neuron loss was observed at nasal levels 4 (11/12, severity 1.4) and 5 (9/12, severity 1.1) and basal cell hyperplasia was observed at nasal levels 4 (10/12, severity 1.8) and 5 (11/12, severity 1.3). At 80 ppm, olfactory neuron loss was observed at levels 3 (8/8, severity 2.4), 4 (12/12, severity 2.4), 5 (11/12, severity 1.5), and 6 (5/12, severity 1.2-incidence not statistically significant) and basal cell hyperplasia was observed at nasal levels 4 (12/12, severity 1.2), 5 (11/12, severity 1.3), and 6 (6/12, severity 1.0).

Dose and end point used for MRL derivation: Two approaches were considered for the derivation of the MRL: the traditional NOAEL/LOAEL approach and the benchmark dose (BMD) modeling approach. For the NOAEL/LOAEL approach, the MRL would be derived using the NOAEL of 10 ppm and LOAEL of 30 ppm for olfactory neuron loss and basal cell hyperplasia in the nasal olfactory epithelium. Two data sets were considered for BMD modeling: olfactory neuron loss and basal cell hyperplasia. Incidence data were reported for nasal section levels 3 (olfactory neuron loss only) through 6. Because the highest incidence of lesions in the 30 ppm group was found in level 4, these data were used for the BMD analyses. The incidence data are reported in Table A-1.

Table A-1. Incidence of Olfactory Neuron Loss ad Basal Cell Hyperplasia Observed in the Nasal Cavity of Male Rats Exposed to Hydrogen Sulfide for 10 Weeks

Concentration (ppm)	Incidence of olfactory neuron loss	Incidence of basal cell hyperplasia
0	0/12	0/12
10	0/12	0/12
30	11/12	10/12
80	12/12	12/12

Source: Brenneman et al. (2000)

The steepness of the dose-response curve for both lesion types (in particular the lack of intermediate response levels) precludes BMD modeling. Therefore, the NOAEL/LOAEL approach was selected for MRL derivation.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a minimal LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:
$NOAEL_{ADJ}$ =10 ppm x 6 hours/24 hours x 7 days/7 days=2.5 ppm

The human equivalent concentration (HEC) was calculated using the following equation (EPA 1994b) for category 1 gases:

$$NOAEL_{HEC} = NOAEL_{ADJ} \times RDGR_{ET}$$

The regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) of 0.184 was calculated using the following equation:

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)_{rat}}{\left(\frac{V_E}{SA_{ET}}\right)_{human}}$$

Where:
V_e is the minute volume and SA_{ET} is the surface area of the extrathoracic (ET) region of the respiratory tract.

Minute volume (V_e)

Human: 13.8 L/minute (EPA 1994b)

Rat: 0.190 L/minute; calculated using the following EPA equation:

$$\ln(V_e) = b_0 + b_1 \ln(BW)$$

For rats, b_0 equals -0.578 and b_1 equals 0.821.

Because limited body weight data were reported in the study, a reference body weight of 0.267 kg (EPA 1988) was used.

EPA (1994b) rat and human respiratory surface area reference values:

Extrathoracic	15.0 cm^2 (rat)	200 cm^2 (human)

$NOAEL_{[HEC]}$ = NOAEL (ADJ) x RGDR = 2.5 ppm x 0.184 = 0.46 ppm

The dosimetric model typically used to estimate a concentration for humans that would be equivalent to the exposure concentration in rats takes into account species differences in the surface area of the upper respiratory tract and inhalation rates. However, the model 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 of the rat nasal epithelium developed for hydrogen sulfide (Moulin et al. 2002; Schroeter et al. 2006a, 2006b) 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 (Schroeter et al. 2006a). Using data generated from hydrogen sulfide uptake simulations in the human nasal passage at exposure levels of 1–50 ppm, Schroeter et al. (2006a) derived regression equations for predicting the maximum and 99th percentile flux values in the human olfactory region. However, data for the uptake simulations in the human nasal passage were based on a model reconstructed from MRI images from one male individual and did not take into account the potential individual variability in parameters. Schroeter et al. (2010) noted that there is considerable variation in nasal anatomy that could affect airflow patterns and dosimetry of inhaled gases. No actual measurements of gas delivery or absorption across nasal membranes were made; the simulations of a single computer model were used by Schroeter et al. (2006a) to predict HECs. When Schroeter et al. (2010) used the same male subject and a different computer model to simulate gas uptake, the average airflux was 14% lower than estimated by Schroeter et al. (2006a). Using MRI data for three adults and two children, Schroeter et al. (2010) concluded that normal variations in nasal anatomy, breathing rate, and air flow distribution were not likely to result in large variations in olfactory wall mass flux of hydrogen sulfide; however, the investigators recommended additional research on the influence of interindividual variability in absorption and pharmacodynamics effects of hydrogen sulfide in the nasal tissues to olfactory dose. Based on these uncertainties in the computational fluid dynamics model to predict a HEC, ATSDR estimated the $NOAEL_{HEC}$ using the dosimetric model, which adjusts for surface area and breathing rate differences between rats and humans.

Was a conversion used from intermittent to continuous exposure? The NOAEL was adjusted for intermittent exposure (6 hours/day, 7 days/week)

Other additional studies or pertinent information that lend support to this MRL: Intermediate-duration animal studies support the identification of the respiratory tract and nervous system as sensitive targets. 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 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 B6C3F1 mice exposed to 30 or 80 ppm; no lesions were observed at 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 lesion 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 B6C3F1 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 6 hours/day, 7 days/week for 2 weeks prior to mating, during mating, on gestation 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.

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated (when appropriate) using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2: "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9: "Interactions with Other Substances," and Section 3.10: "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically the levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2: "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4: "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

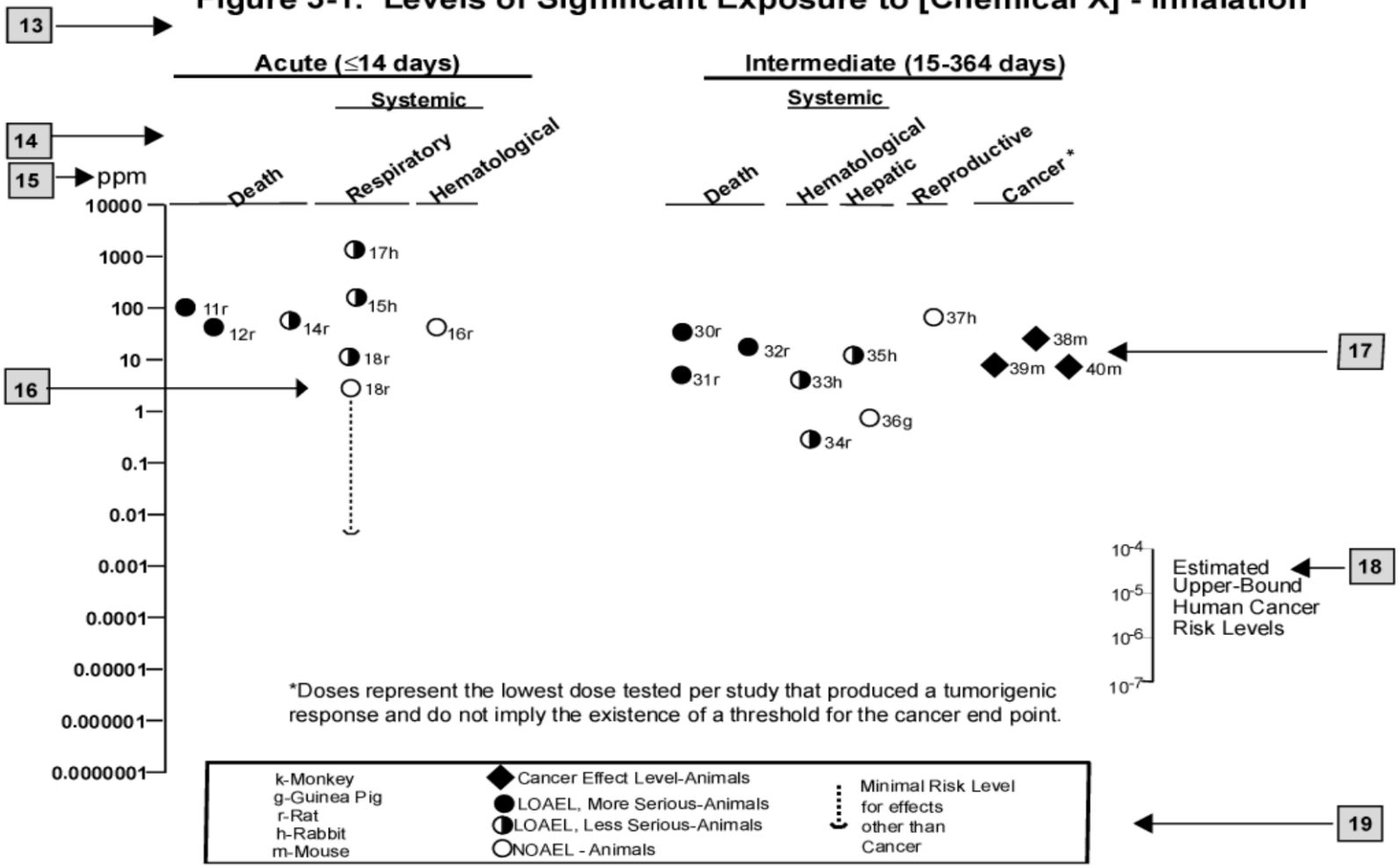
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

APPENDIX C

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans*,*trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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APPENDIX D. INDEX